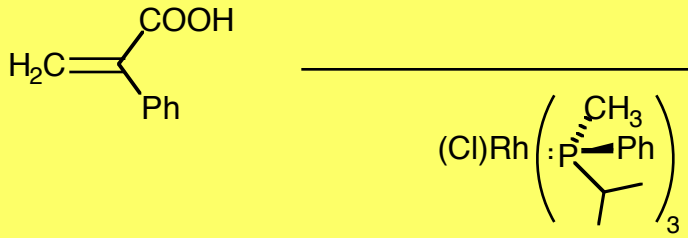
Asymmetric Hydrogenation with Chiral Iridium Catalysts

Andreas Pfaltz

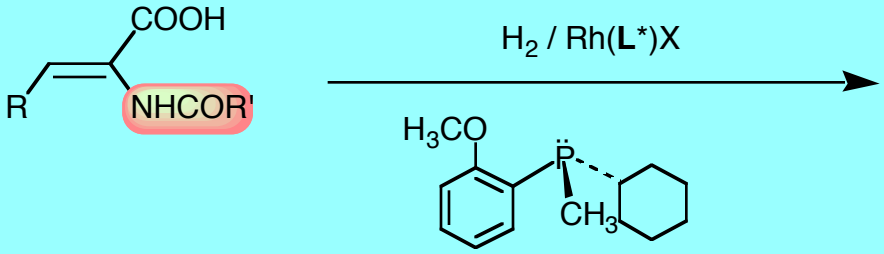
Department of Chemistry, University of Basel

ENANTIOSELECTIVE HYDROGENATION

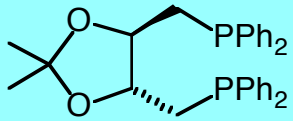


~15 % ee

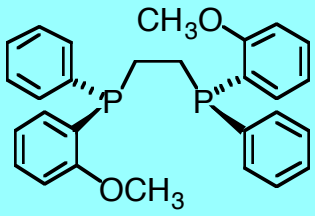
HORNER et al. (1968)
KNOWLES & SABACKY (1968)



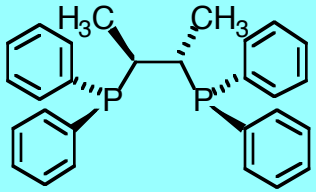
88 % ee — KNOWLES et al. (1970)



DIOP — ~ 70 % ee — KAGAN & DANG (1971)

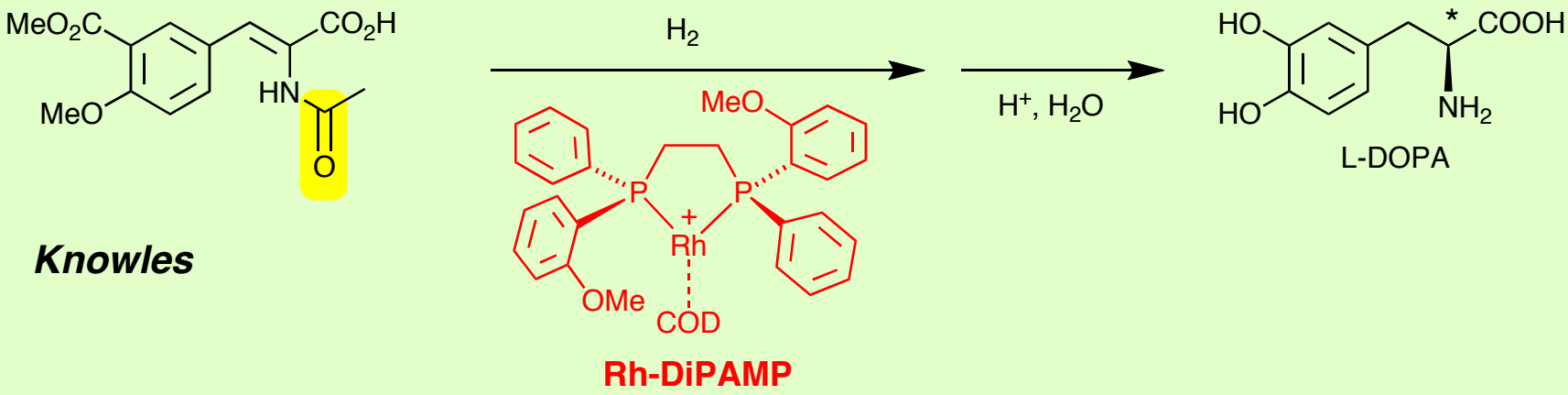


DIPAMP — 96 % ee — KNOWLES et al. (1974)



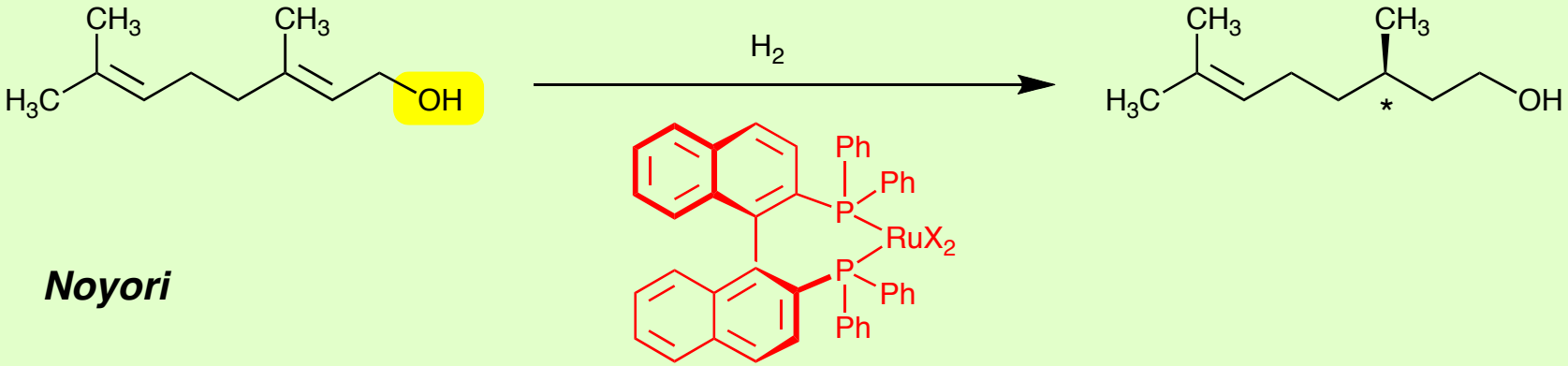
CHIRAPHOS — ~100 % ee — BOSNICH & FRYZUK (1977)

Asymmetric hydrogenation of functionalized olefins



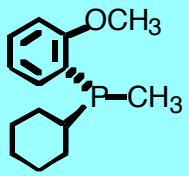
Knowles

Rh-DiPAMP

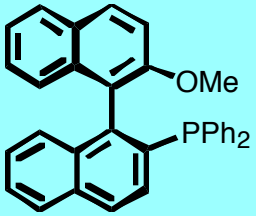


Noyori

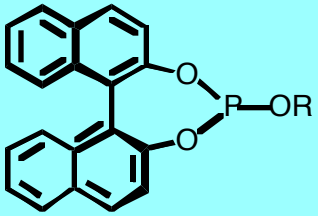
Ru-BINAP

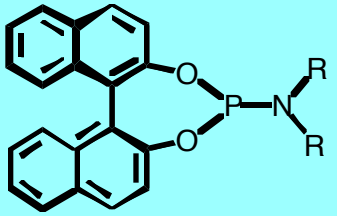


CAMP

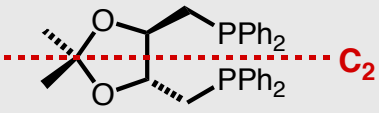


MOP

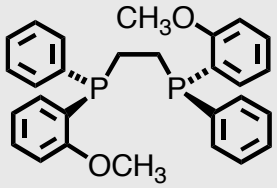




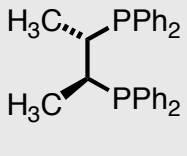
MonoPhos



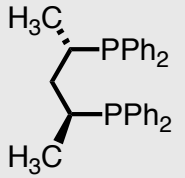
DIOP



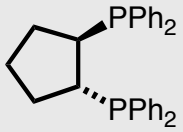
DIPAMP



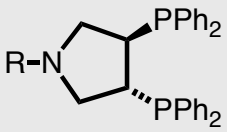
Chiraphos



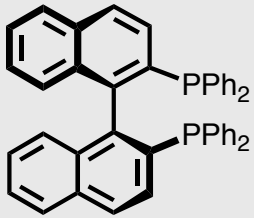
Skewphos



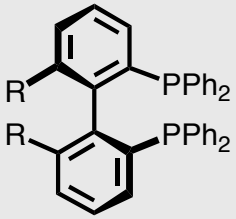
DPCP



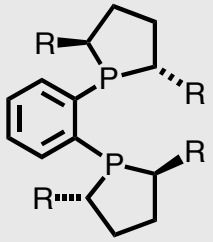
Pyrphos
Deguphos



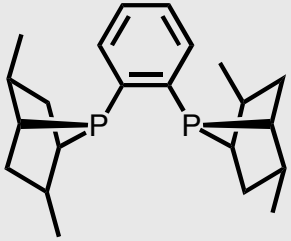
BINAP



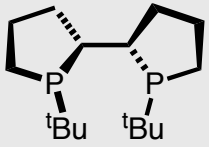
BIPHEP



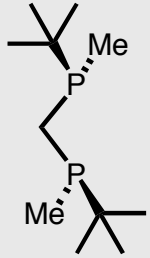
Duphos



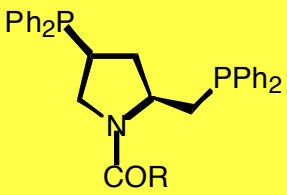
PennPhos



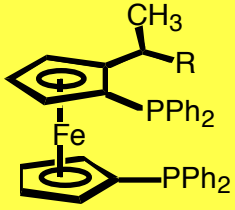
TangPhos



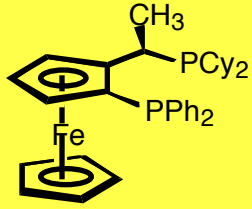
MiniPHOS



BPPM (R=O*t*-Bu)



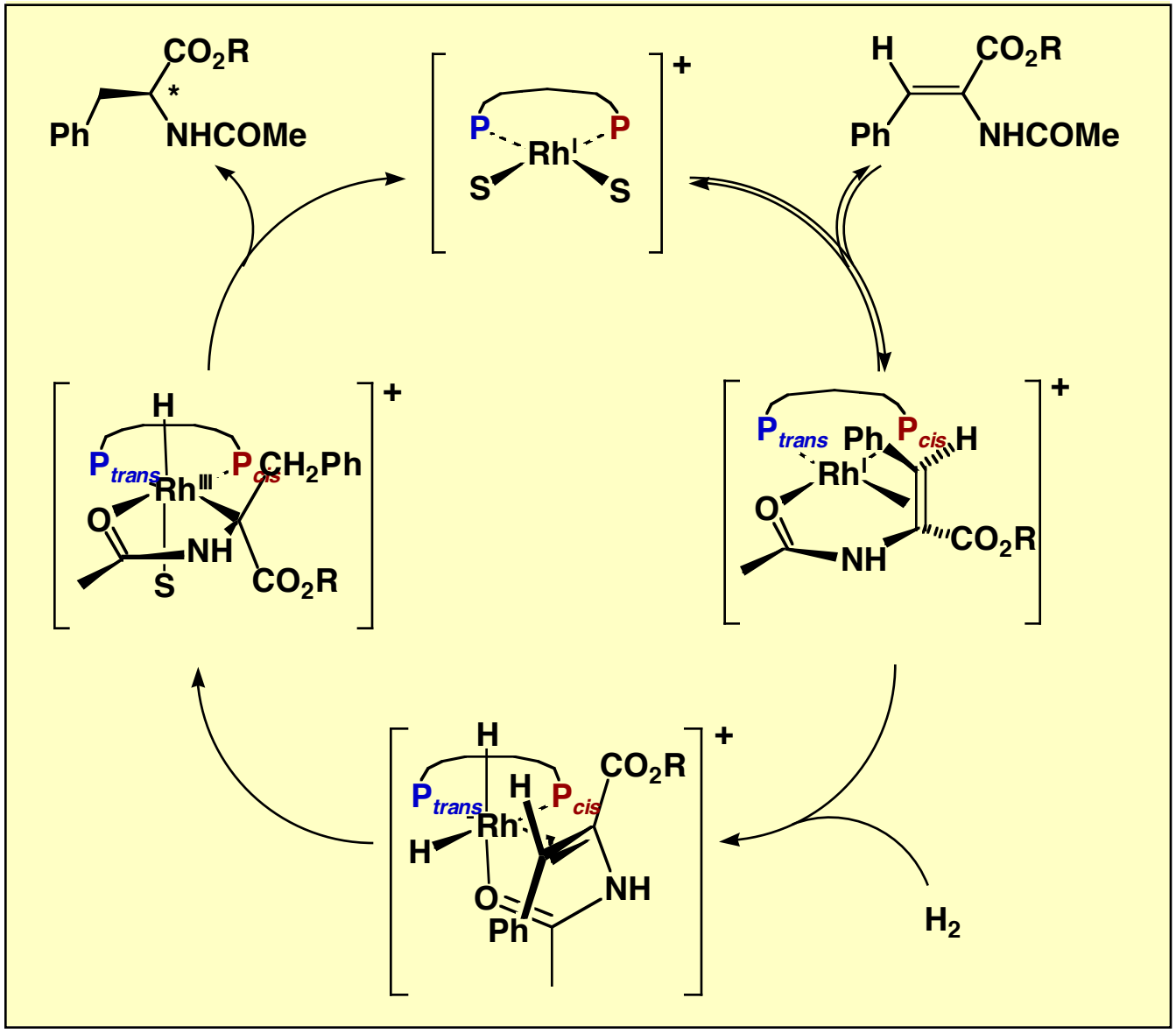
BPPFA (R=NMe_2)



Josiphos

Achiwa's "Respective Control Concept"

Synlett **1992**, 169



P_{trans} and P_{cis} have different steric and electronic interactions with the substrate

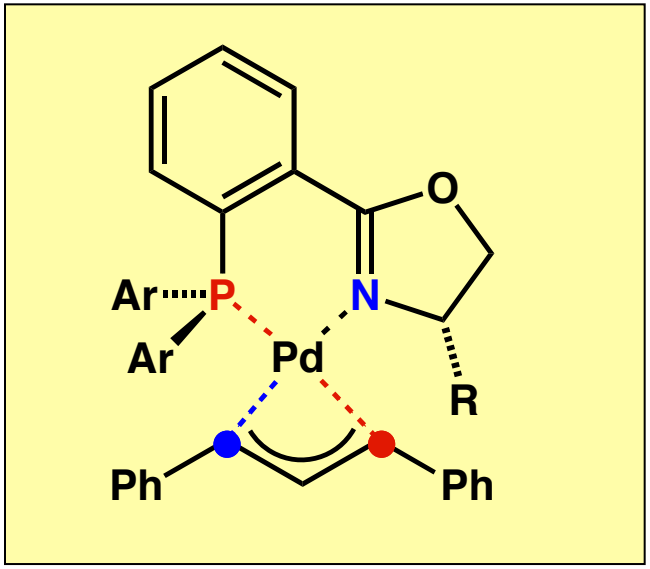
⇩

P_{trans} and P_{cis} have different effects on the **enantioselectivity** and **rate**

⇩

P_{trans} and P_{cis} groups must perform different functions and, therefore, **should be optimized individually**.

Phosphinooxazolines (PHOX ligands)



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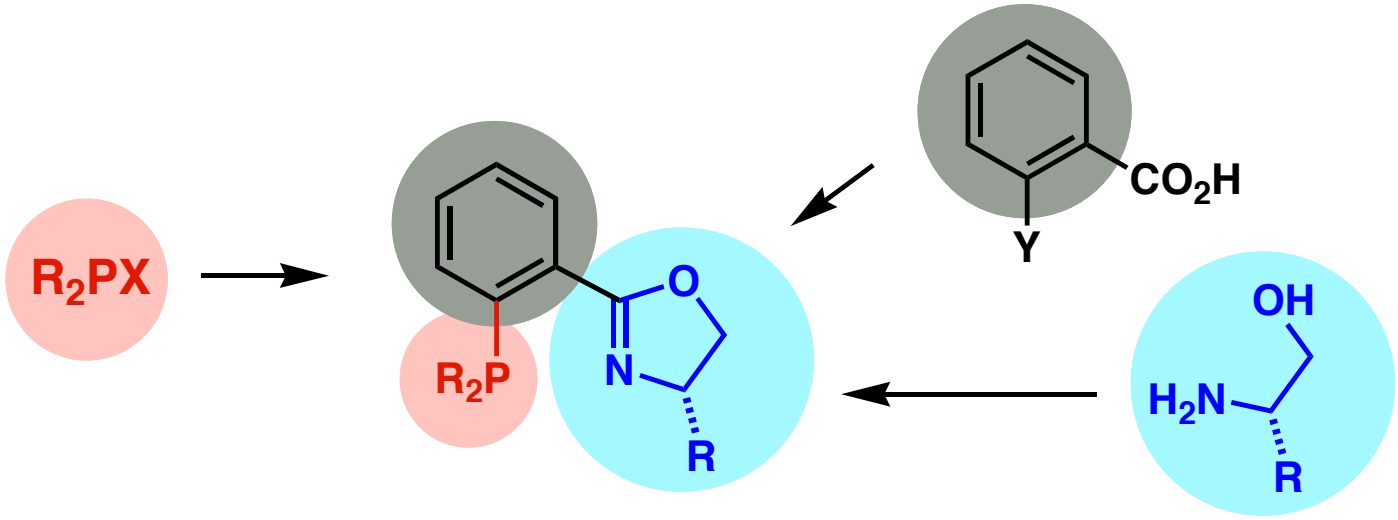
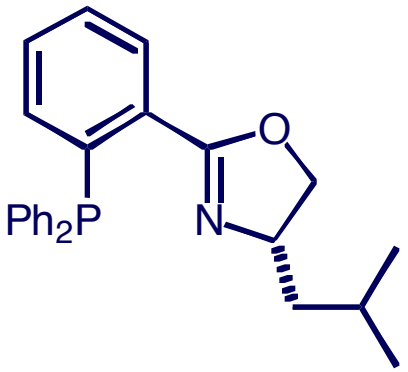
Angew. Chem. Int. Ed. **1993**, *32*, 566

J. Sprinz, G. Helmchen
Tetrahedron. Lett. **1993**, *34*, 1769

G. J. Dawson, C. G. Frost, J. M. J. Williams,
S. J. Coote, T*etrahedron. Lett.* **1993**, *34*, 3149

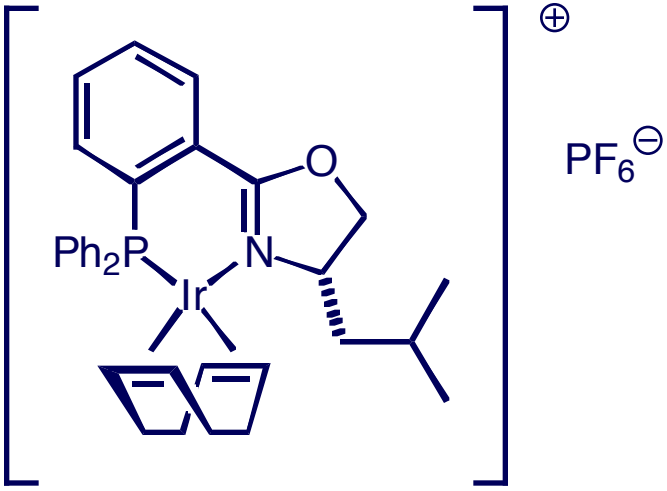


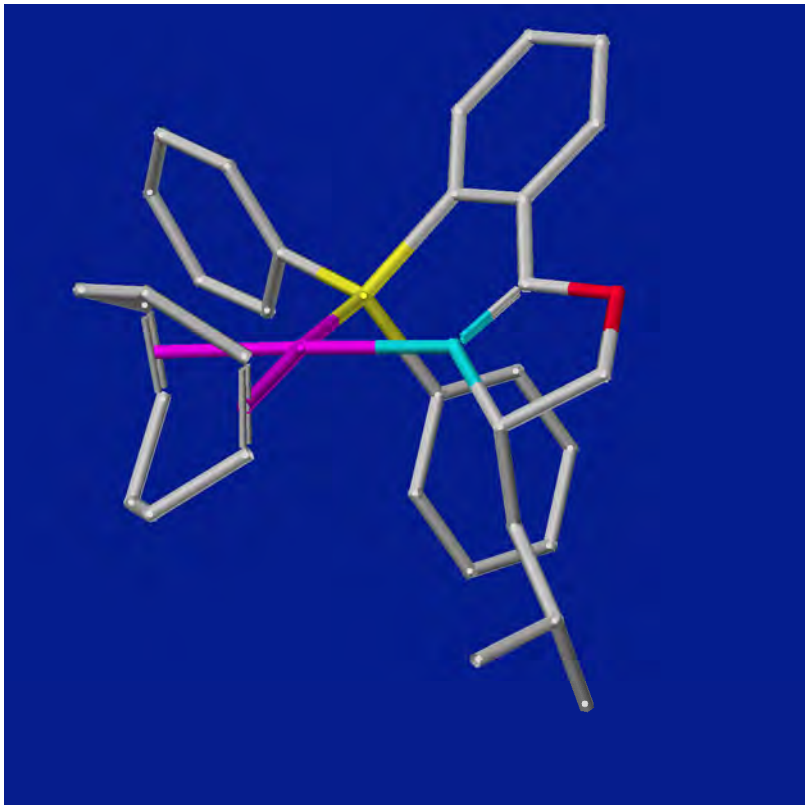


1) $[Ir(COD)Cl]_2$, CH_2Cl_2, reflux

2) NH_4PF_6, H_2O / CH_2Cl_2

3) crystallization (CH_2Cl_2 / Et_2O)



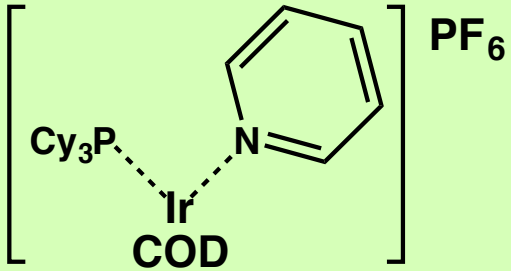


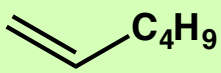
X-RAY ANALYSIS

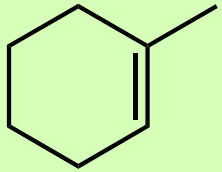
Ludwig Macko, Prof.
Margareta Zehnder
(University of Basel)

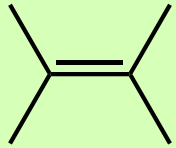
Olefins without coordinating groups

Crabtree



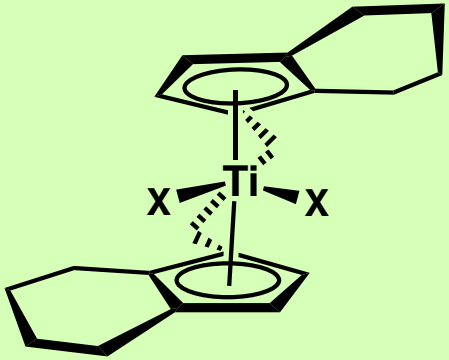


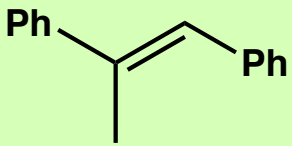




TOF (h^{-1}) 6400 3800 4000

Buchwald



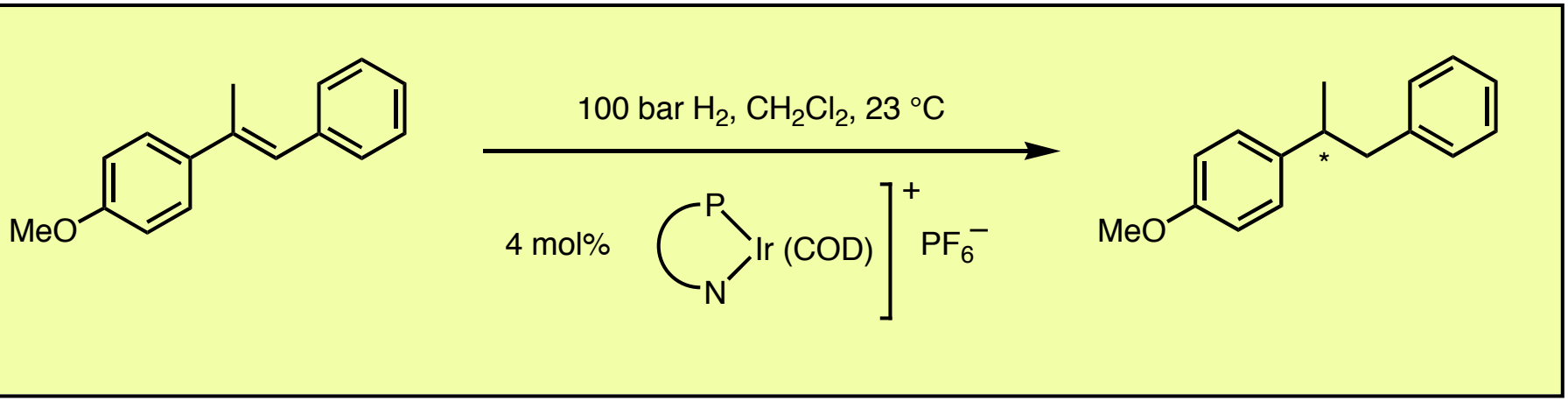


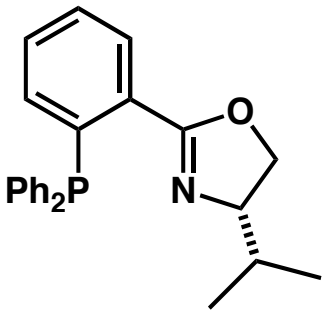
94% yield
99% ee

High yield and ee
5-8 mol% catalyst
low TOF (1-2 h^{-1})

Broene & Buchwald, *JACS* **1993**, *115*, 12569

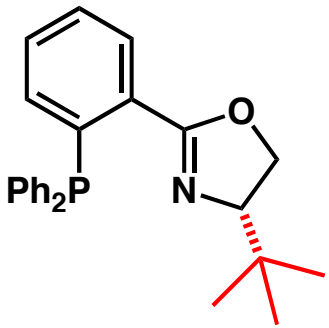
Initial Experiments





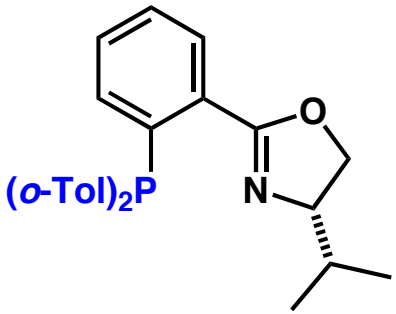
78% conv.

75% ee



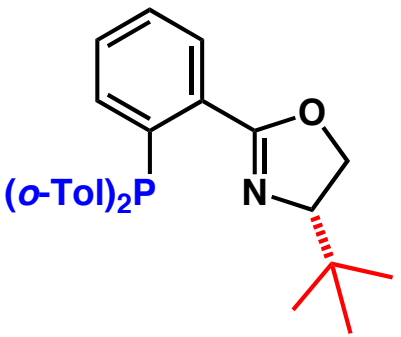
98% conv.

90% ee



100% conv.

91% ee

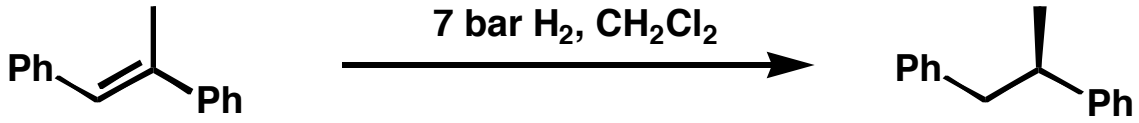


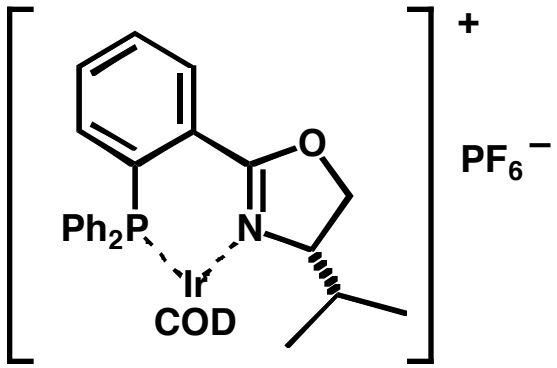
72% conv.

97% ee

PATRICK SCHNIDER, ANDREW LIGHTFOOT

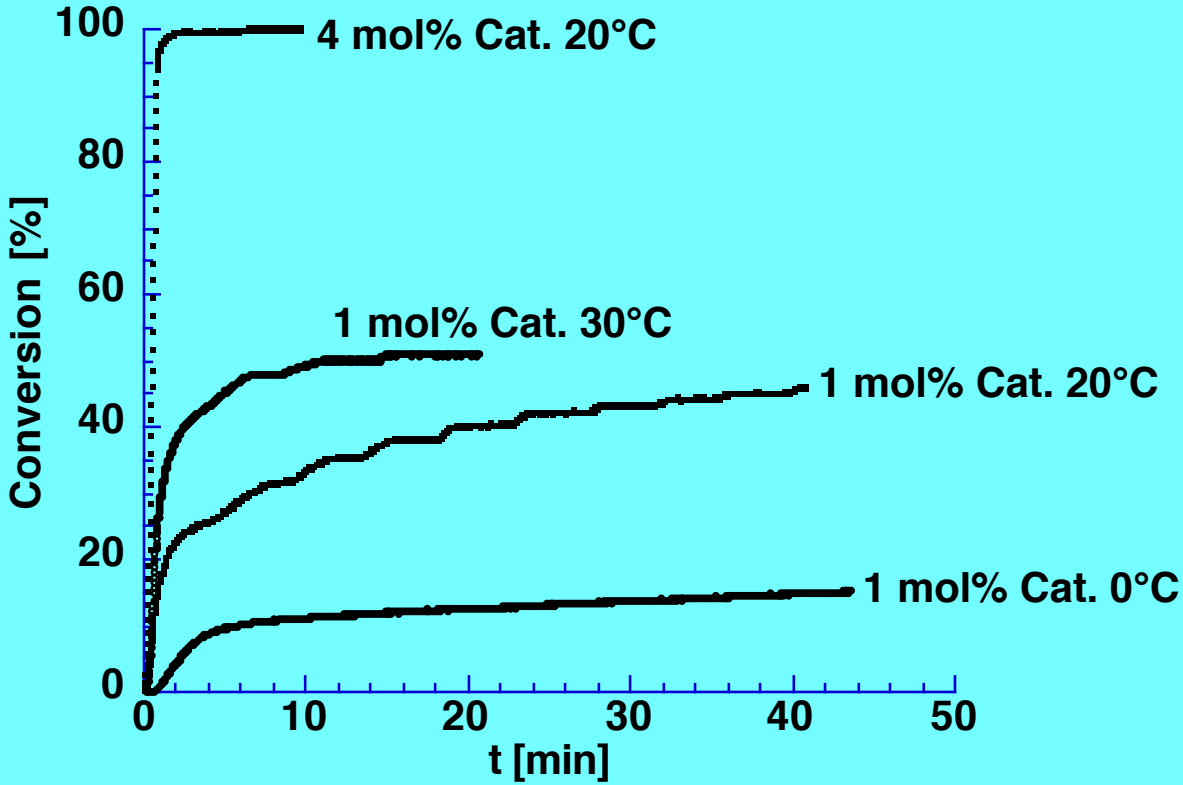
Kinetic Studies



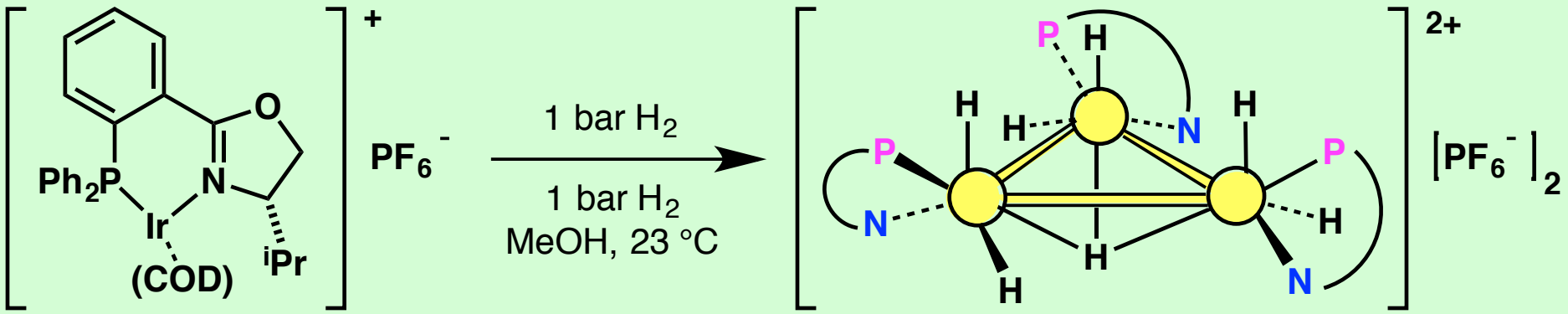


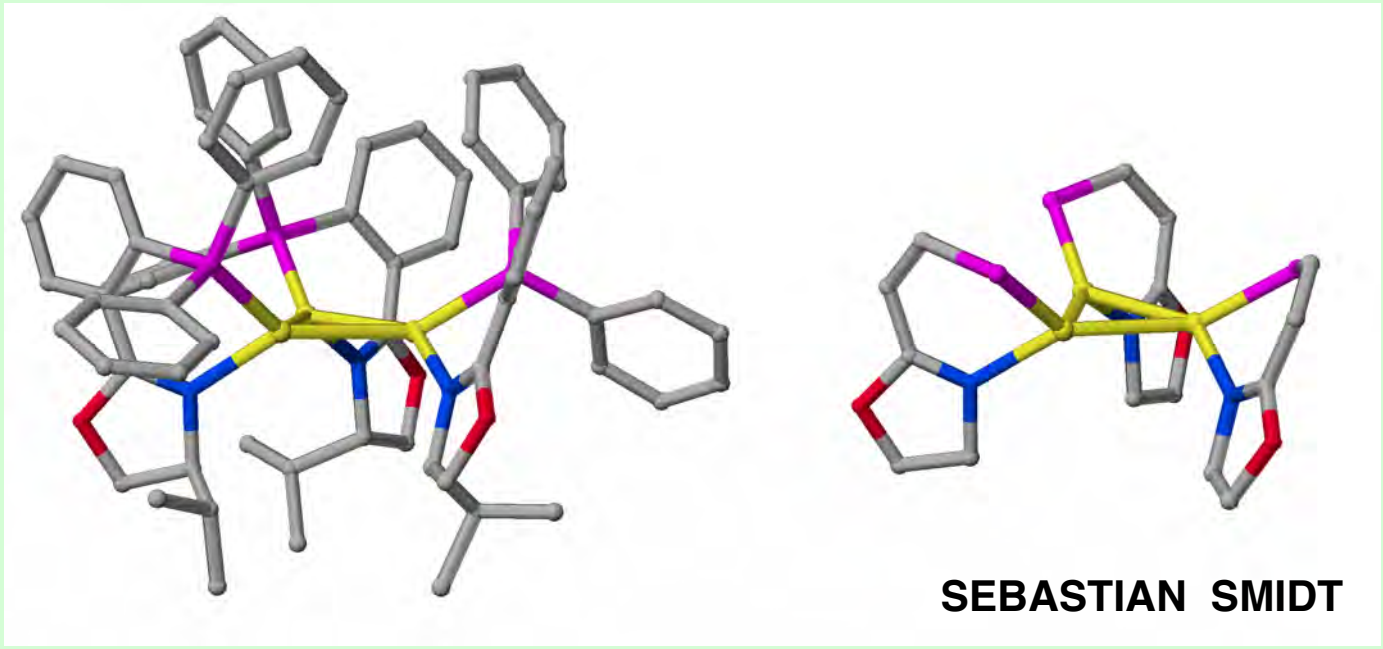
catalyst

Prof. Donna G. Blackmond
Thorsten Rosner
(MPI für Kohlenforschung)

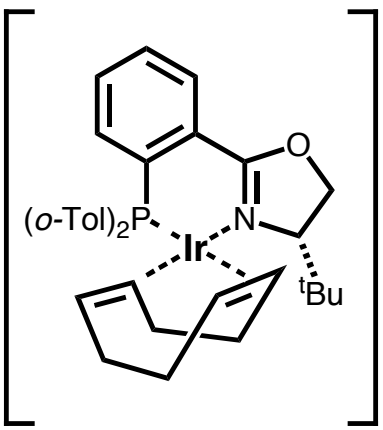


Preparation and X-ray analysis of the trinuclear complex $[\{Ir(PHOX)H_2\}_3H]\,[PF_6]_2$

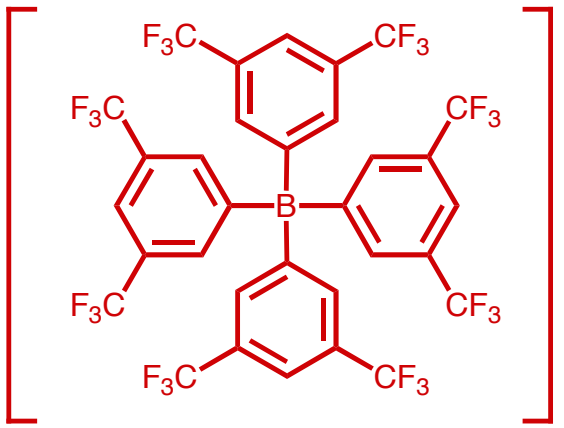




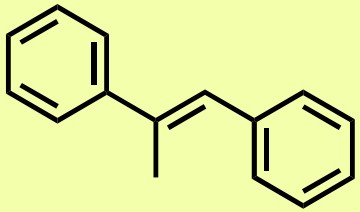
Effect of the anion



$X^{\ominus}$ $X^{\ominus}$ = $[PF_6]^{\ominus}$ or

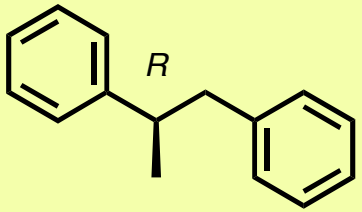


BAr_F



Cat.

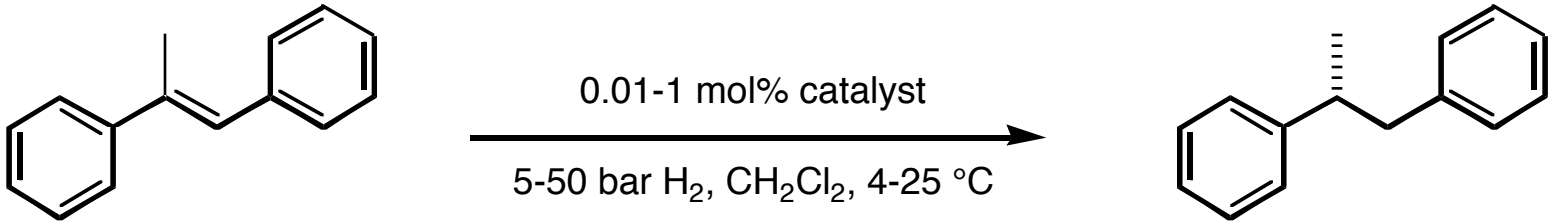
10 bar H_2
CH_2Cl_2, 23 °C

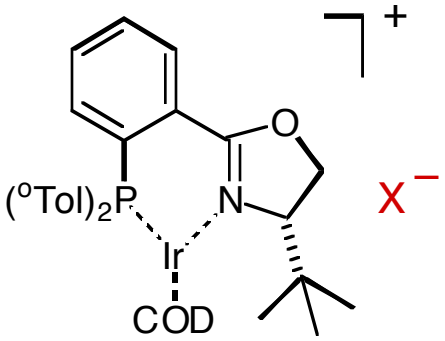


X = PF_6:	1 mol% catalyst	~ 50% conversion	97% ee	TOF 2400 h^{-1}
X = BAr_F:	0.02 mol% catalyst	99% conversion	98% ee	TOF > 5000 h^{-1}

Andrew Lightfoot

KINETIC STUDIES

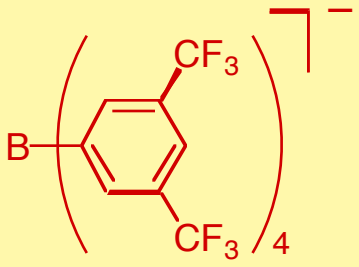




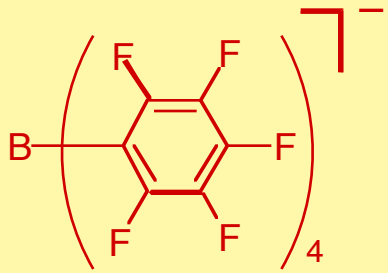
catalyst

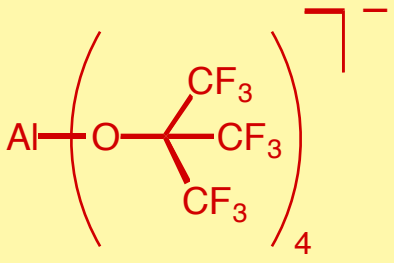
SEBASTIAN SMIDT

Anions: BF_4^-, PF_6^-, $CF_3SO_3^-$



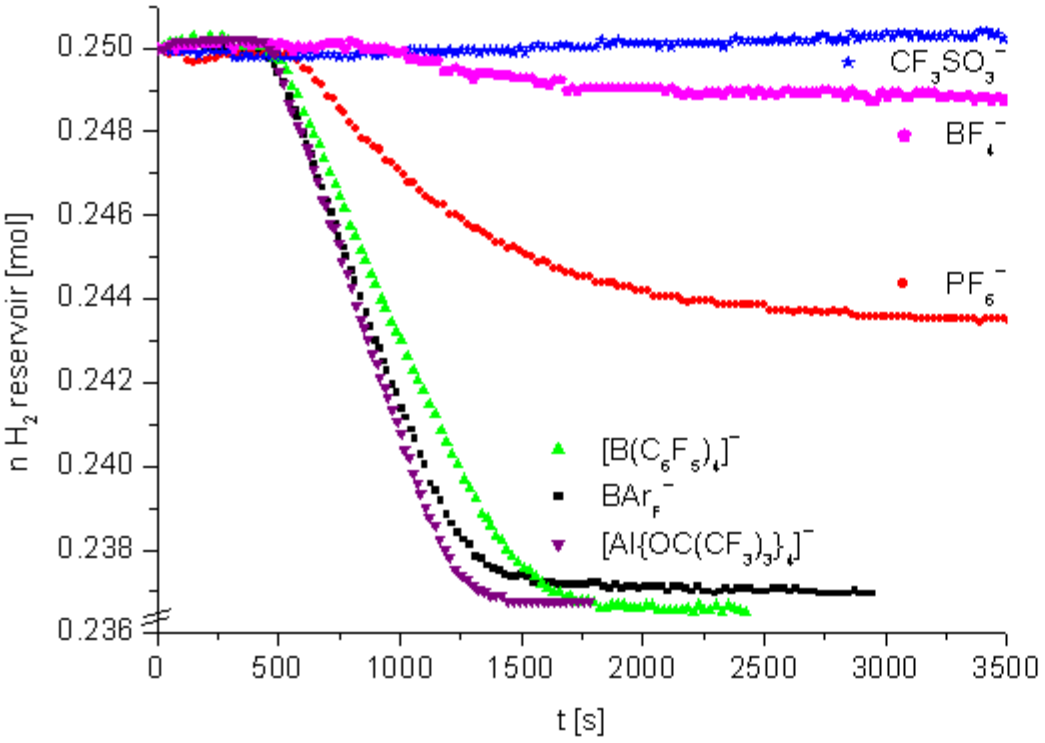
BAr_F





Ingo Krossing
(Univ. of Karlsruhe)

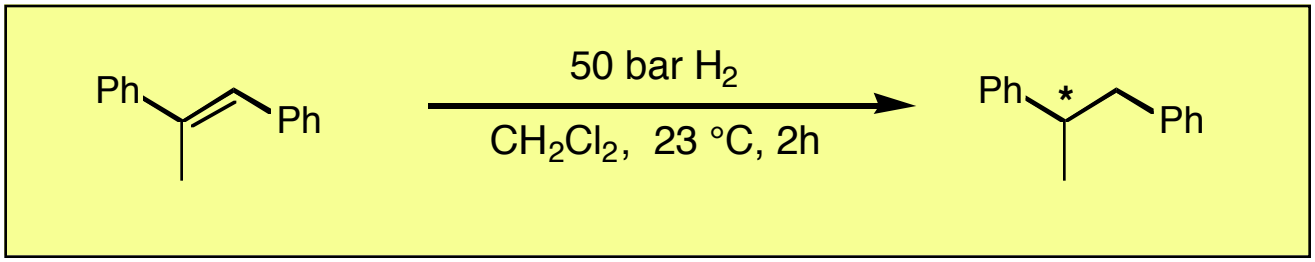
Catalysts with Six Different Anions



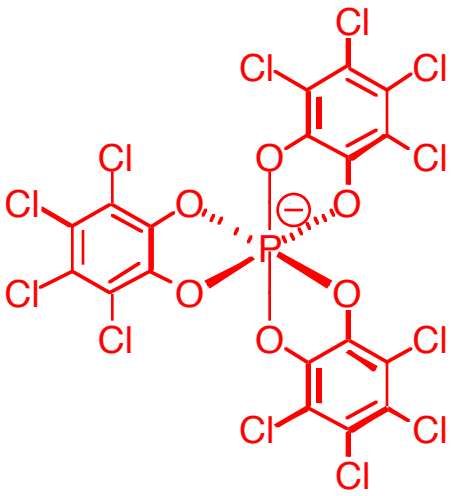
anion	v_{max} [mmol min^{-1}]	conversion (GC) [%]
$[Al\{OC(CF_3)_3\}_4]^-$	1.085	>99
BAr_F^-	0.993	>99
$[B(C_6F_5)_4]^-$	0.829	>99
PF_6^-	0.368	52
BF_4^-	0.067	13

all 0.1 mol% at 14 bar H_2 and 4 °C in CH_2Cl_2

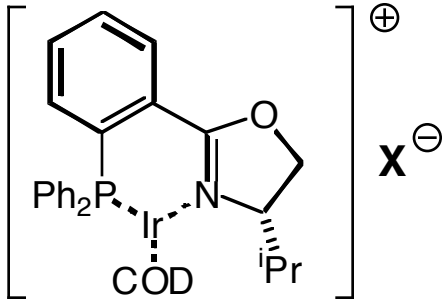
$$[Al\{OC(CF_3)_3\}_4]^- > BAr_F^- > [B(C_6F_5)_4]^- > PF_6^- >> BF_4^- > CF_3SO_3^-$$



Δ-TRISPHAT:

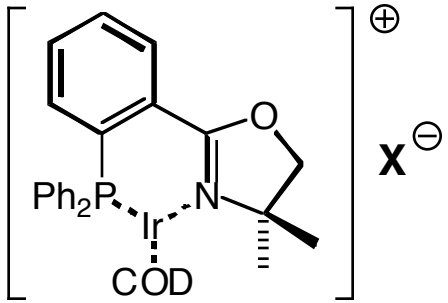


Jérôme Lacour
(University of Geneva)



X = BAr_F: **70% ee**
(1 mol% cat.) **100% conv.**

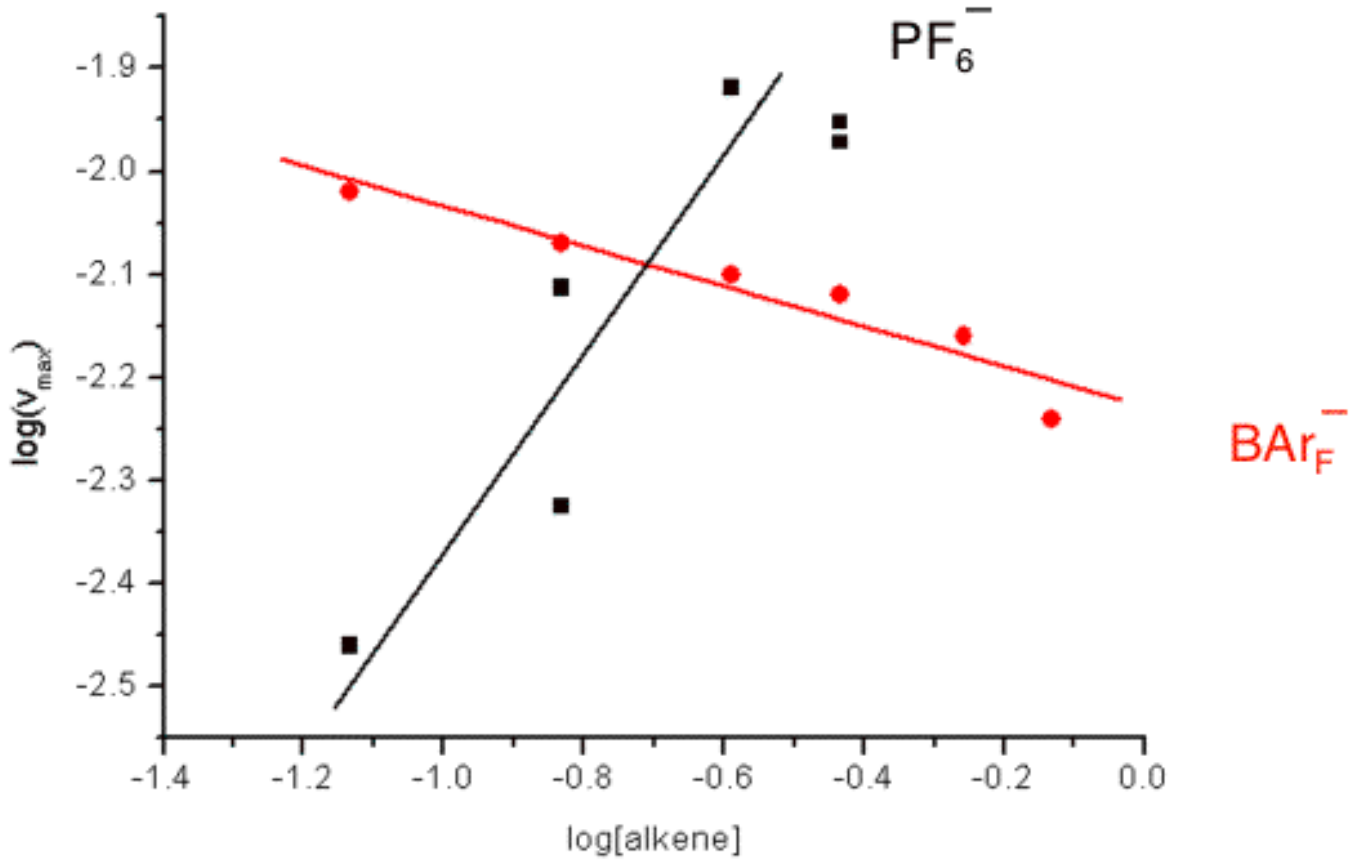
X = Δ-TRISPHAT: **70% ee**
(4 mol% cat.) **100% conv.**



X = Δ-TRISPHAT: **0% ee**
(4 mol% cat.) **100% conv.**

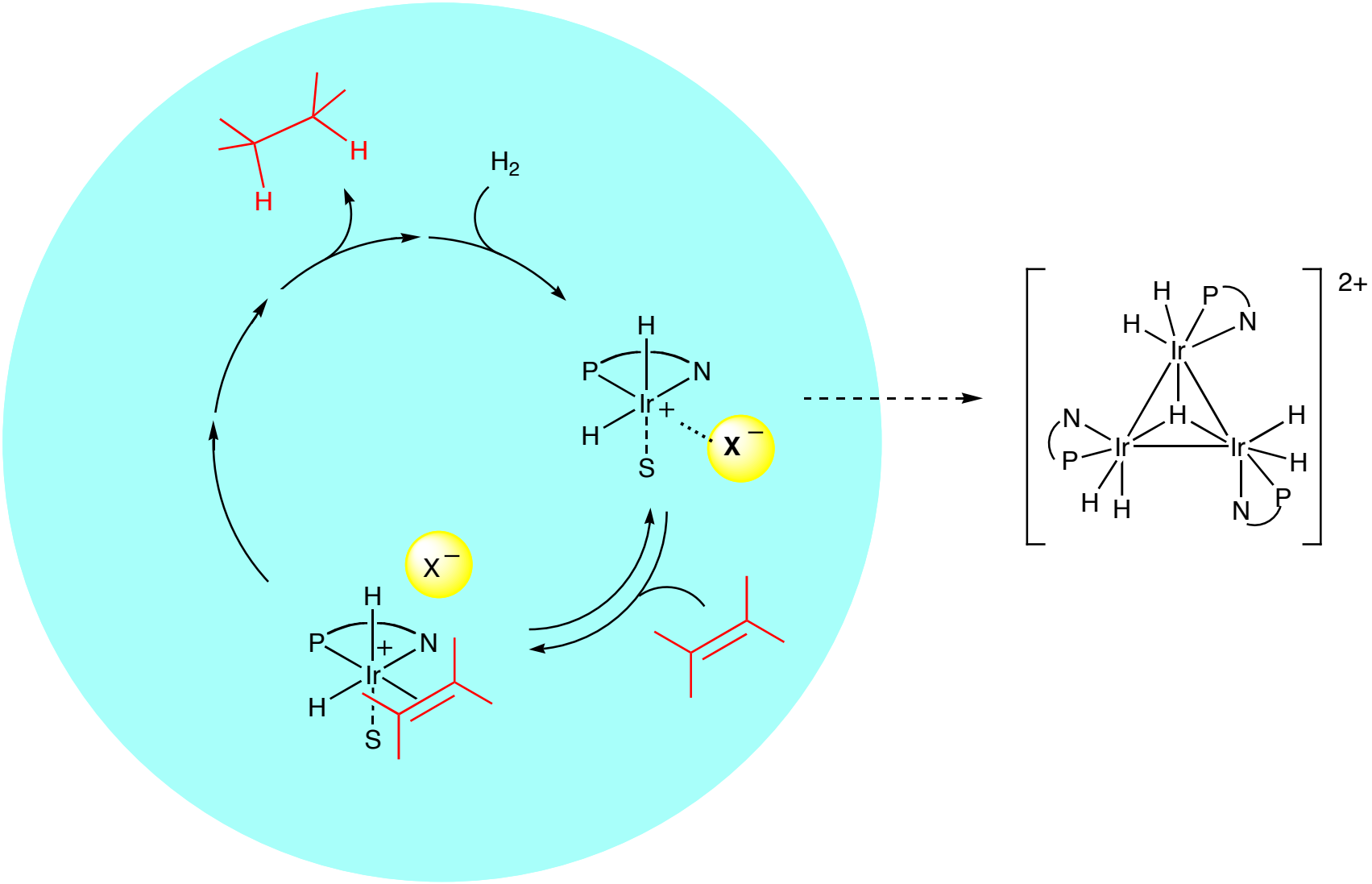
X = Δ-TRISPHAT: **0% ee**
(1 mol% cat.) **70% conv.**

Dependence of v_{max} on Alkene Concentration

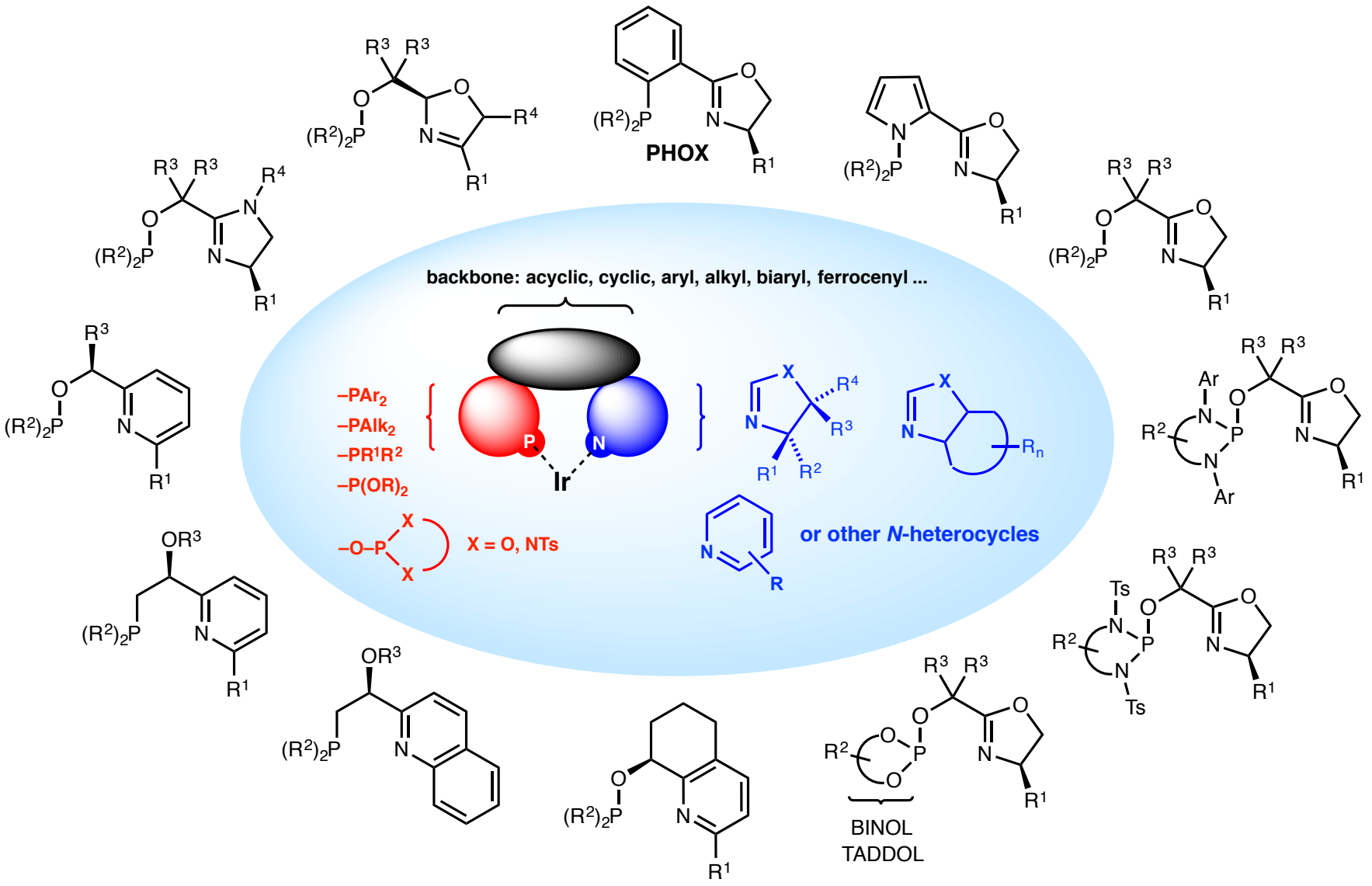


Anion	BAr_F^-	PF_6^-
Rate Order	– 0.2	1.0

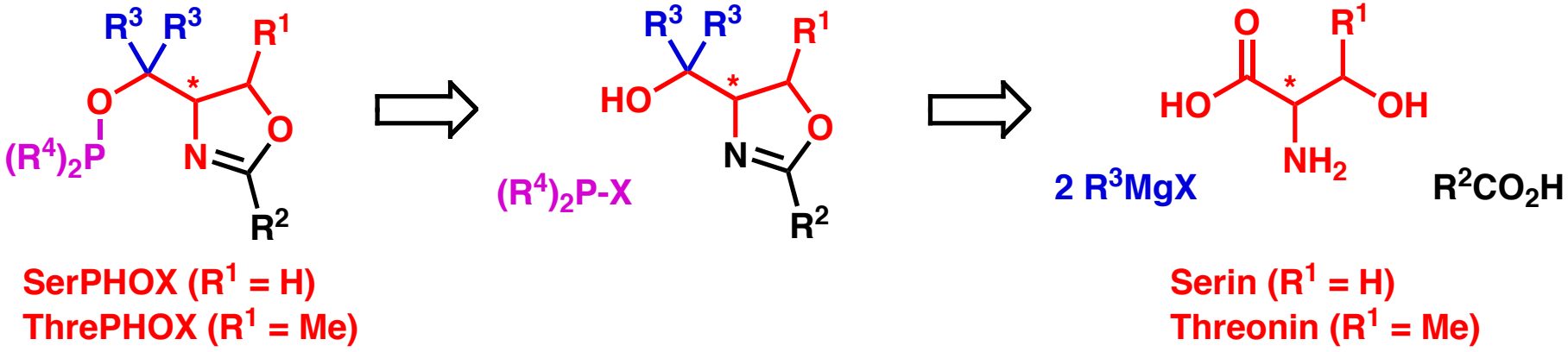
Hydrogenation vs. catalyst deactivation: influence of the anion



Variation of the Catalyst Structure



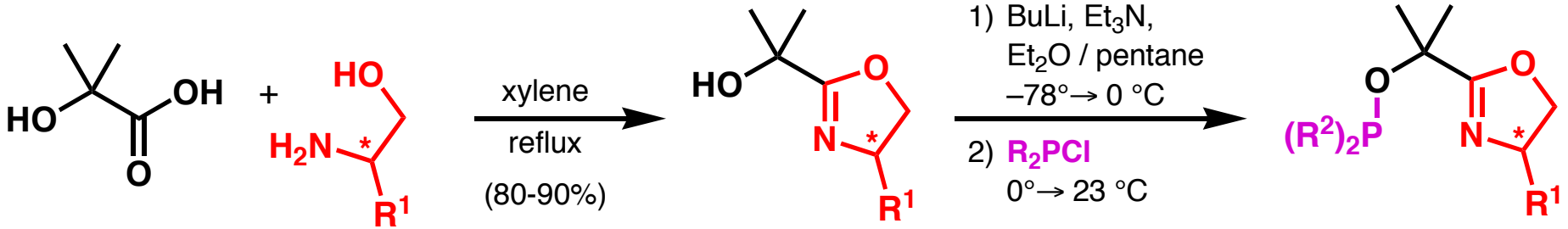
Variation of the Phosphinooxazoline Structure



SerPHOX (R^1 = H)
ThrePHOX (R^1 = Me)

Serin (R^1 = H)
Threonin (R^1 = Me)

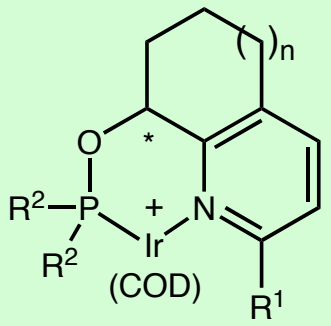
Jörg Blankenstein, Frederik Menges



SimplePHOX

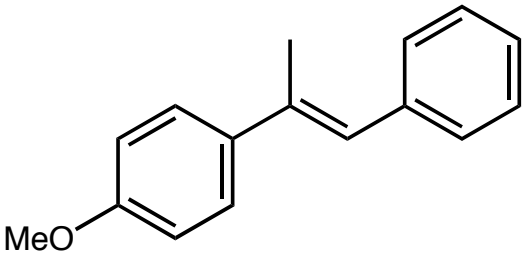
Sebastian Smidt

Pyridine-Phosphinite Ligands

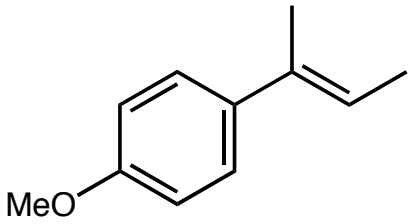


1 n = 0 R^1 = Ph R^2 = tBu
2 n = 0 R^1 = Ph R^2 = oTol
3 n = 1 R^1 = H R^2 = tBu

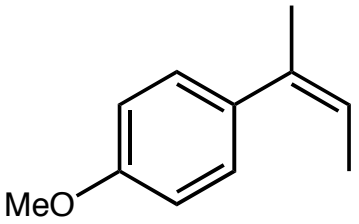
1 mol% catalyst, CH_2Cl_2, 50 bar H_2, RT



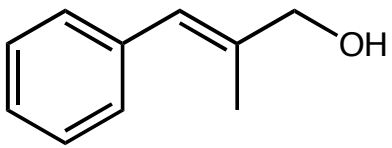
2: 99.9% ee



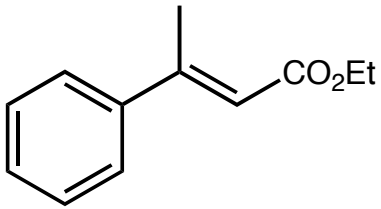
1: 99.5% ee



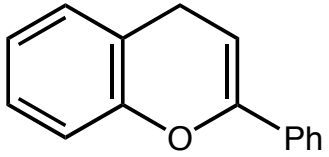
2: 98% ee



2: 95% ee



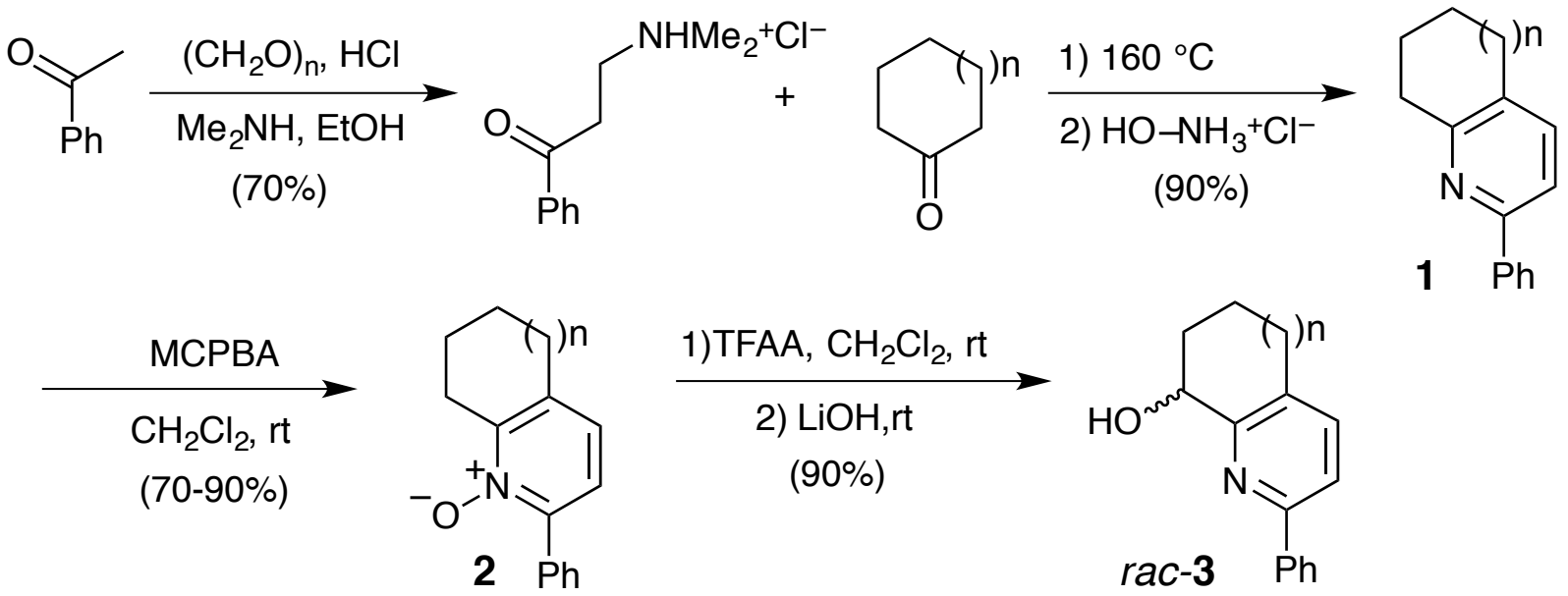
1: >99% ee

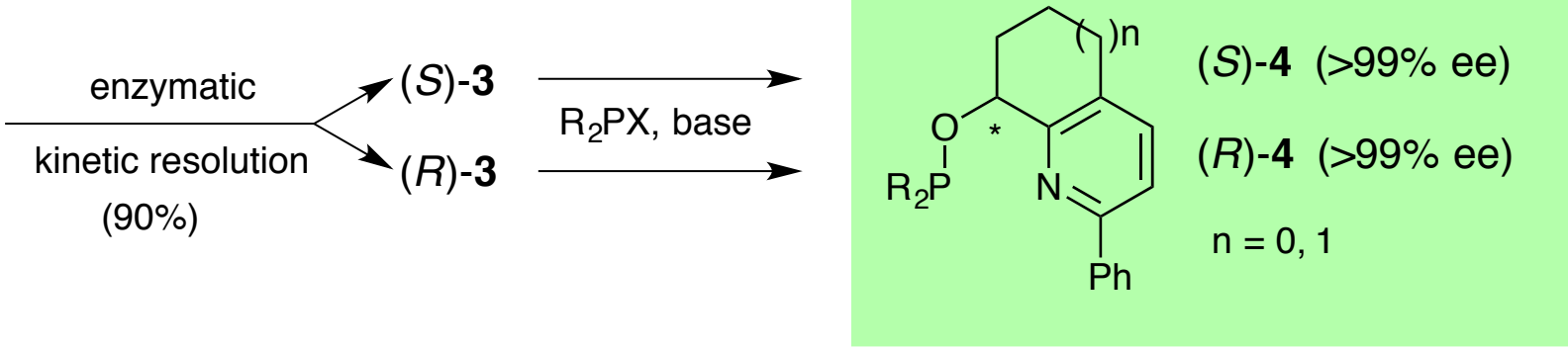


1: 98% ee

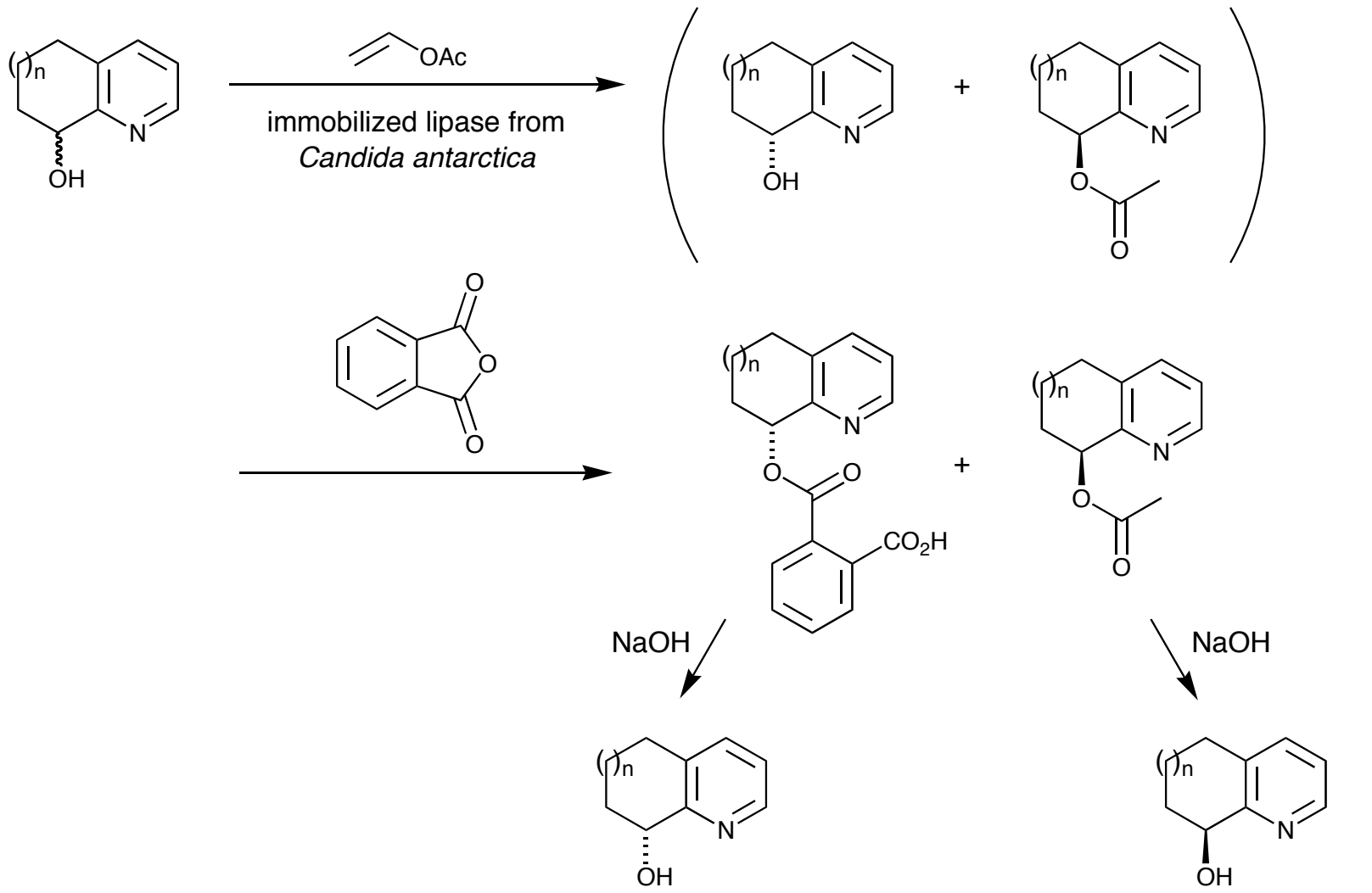
Stefan Kaiser

Synthesis of Bicyclic Pyridine-Phosphinite Ligands



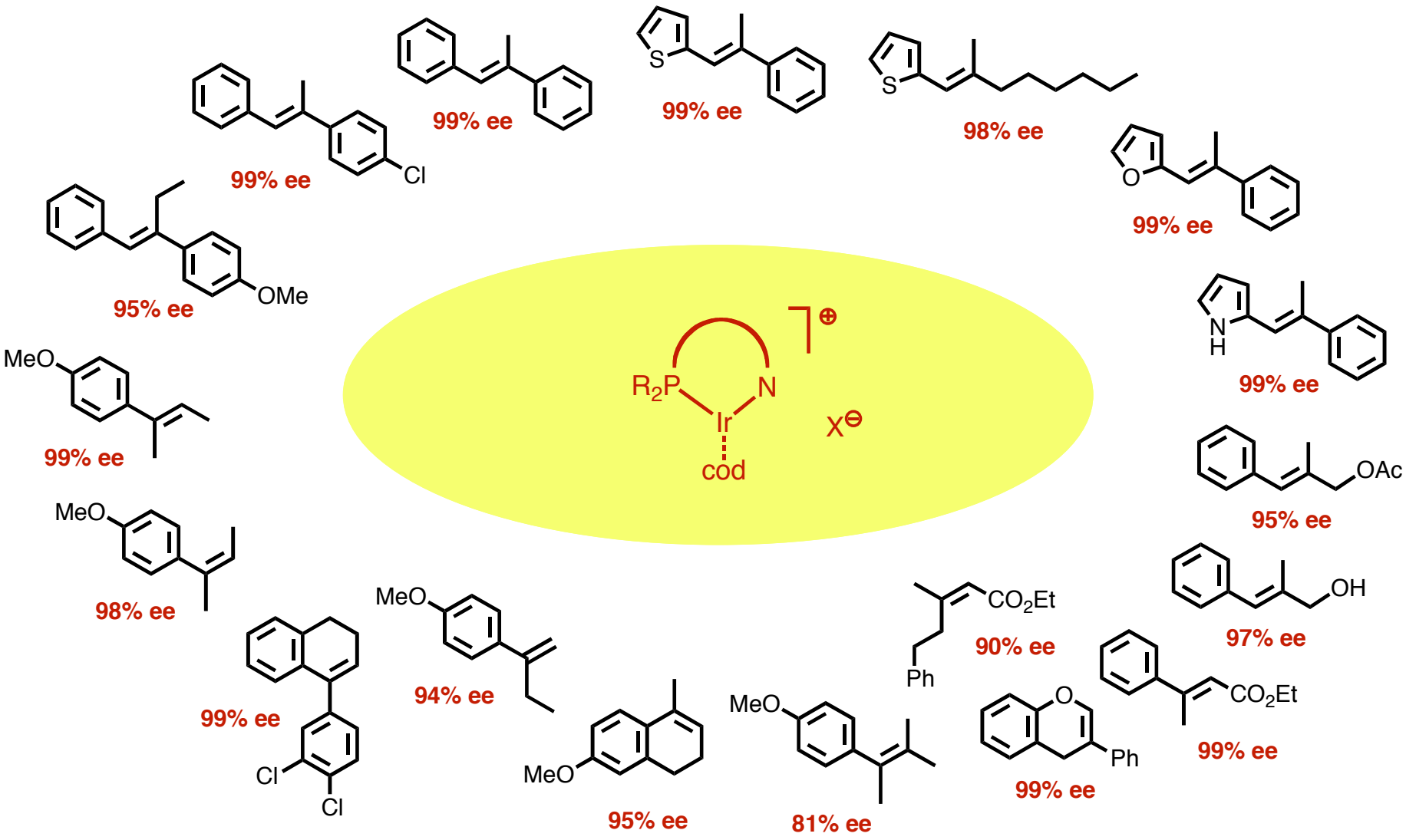


Practical chromatography-free kinetic resolution with lipase



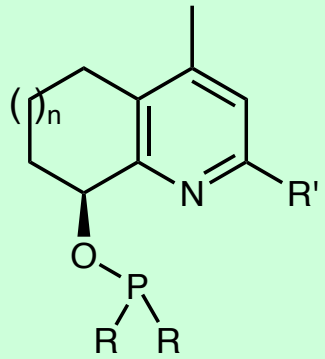
Matthias Maywald

Synthesis **2009**, 3654

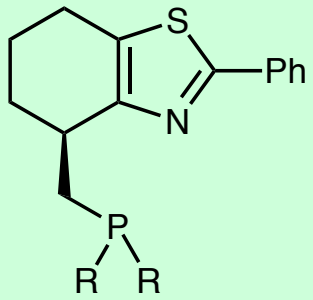

99% ee
99% ee
99% ee
98% ee
99% ee
Cl
99% ee
OMe
95% ee
MeO
99% ee
MeO
98% ee
R2P
N
Ir
cod
X⊖
⊕
N
H
99% ee
OAc
95% ee
OH
97% ee
CO2Et
90% ee
Ph
MeO
94% ee
99% ee
Cl
Cl
MeO
95% ee
MeO
81% ee
O
Ph
99% ee
CO2Et
99% ee

Contributions of other groups

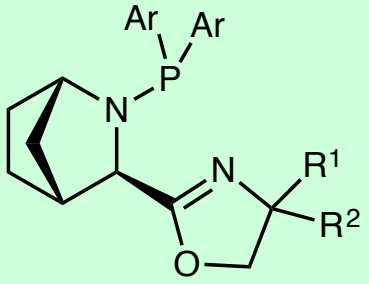
P,N:



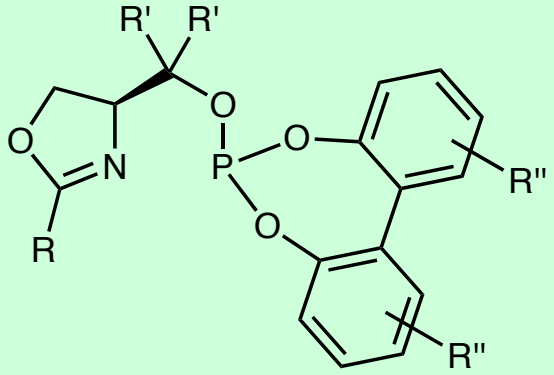
Yon-Gui Zhou
Tet. Lett. **2006**, *47*, 4733



Andersson
JACS **2006** *128*, 2995

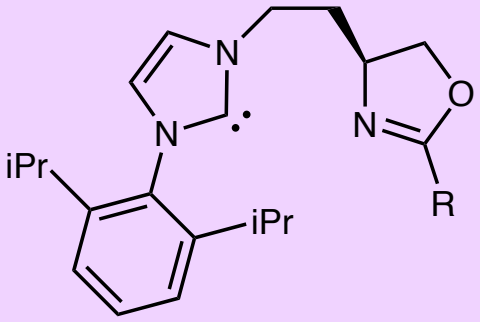


Andersson
JACS **2008**, *130*, 5595



Diéguez, Pàmies, *JACS* **2009**, *131*, 12344

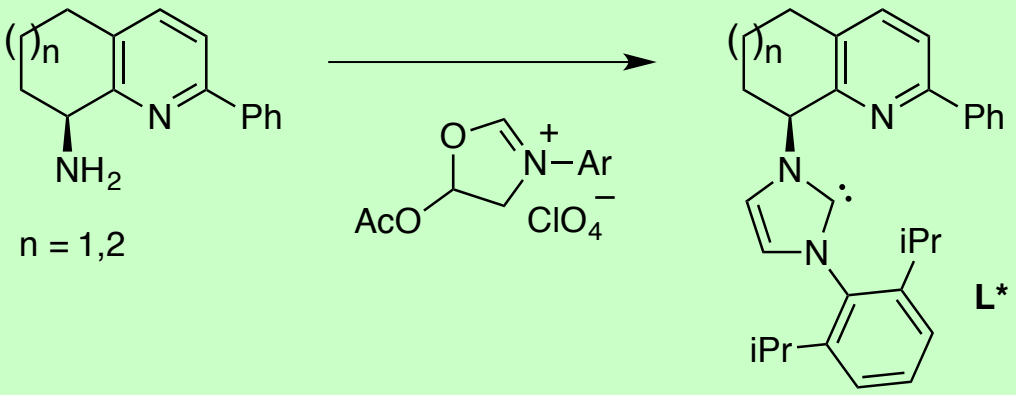
C,N:

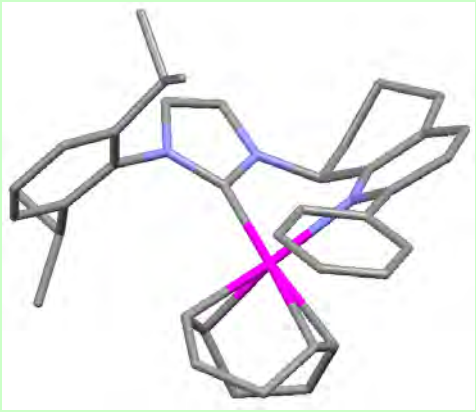


R = 1-adamantyl

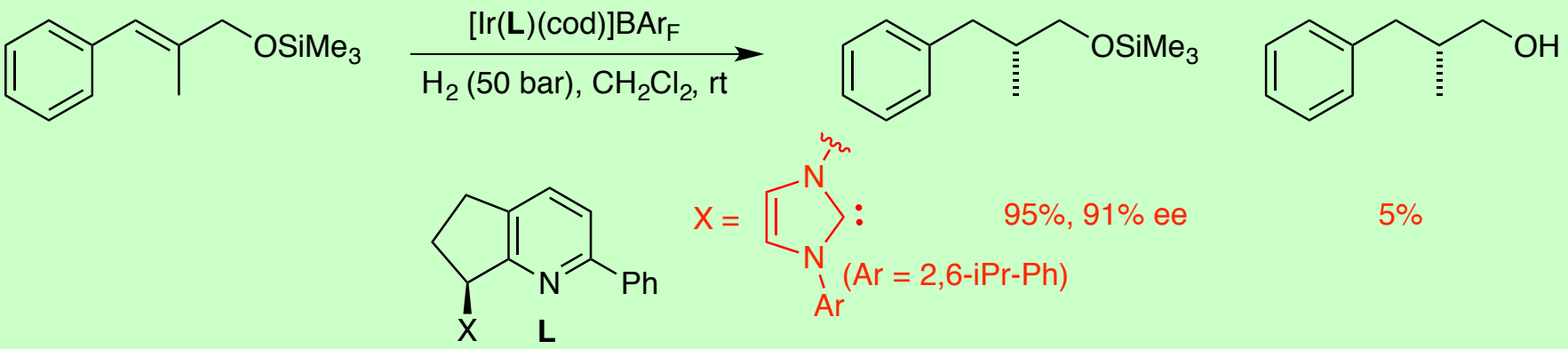
Burgess, *JACS* **2001**, *123*, 8878

NHC-Pyridine Ligands



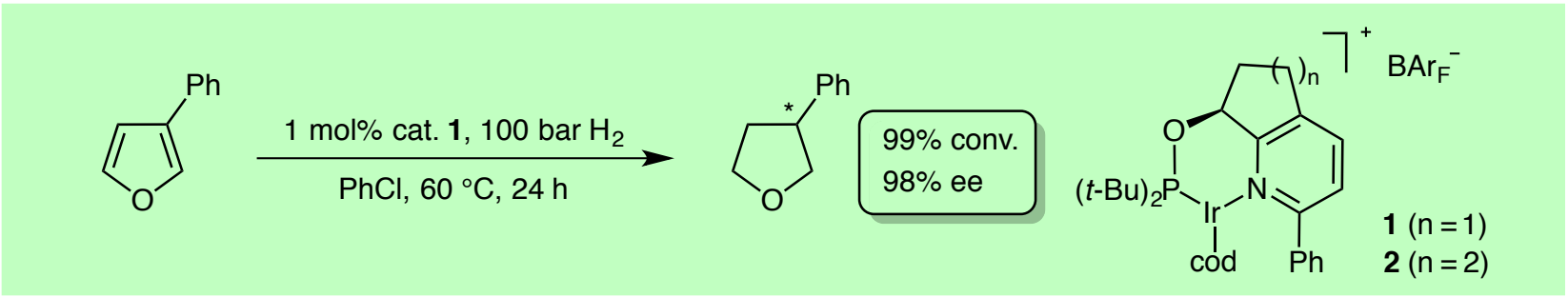


[IrL*(cod)]BAr_F

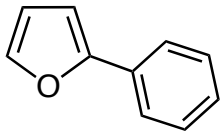


Andreas Schumacher

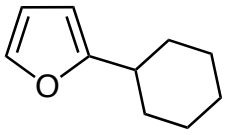
Asymmetric hydrogenation of furans and benzofurans



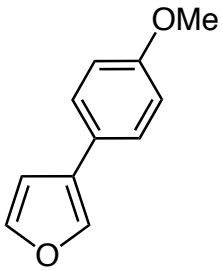
*Hydrogenation of furans with catalyst **1**:*



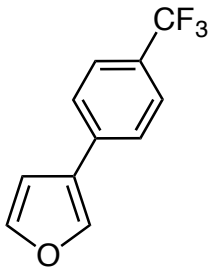
15% conv.
2% ee



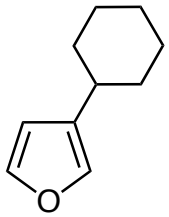
96% conv.
82% ee



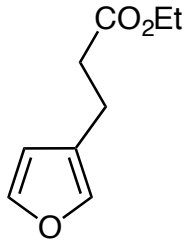
83% conv.
95% ee



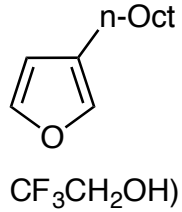
88% conv.
97% ee



>99% conv.
98% ee

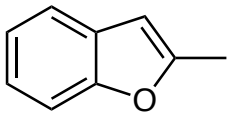


>99% conv.
93% ee

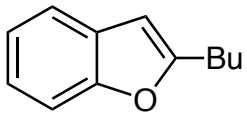


94% conv.
95% ee

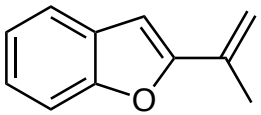
*Hydrogenation of benzofurans with catalyst **1**:*



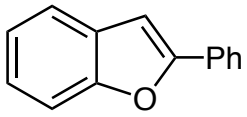
93% conv.
98% ee



99% conv.
99% ee

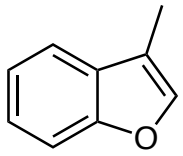


99% conv.
97% ee



4% conv.
0% ee

*Catalyst **2**:*

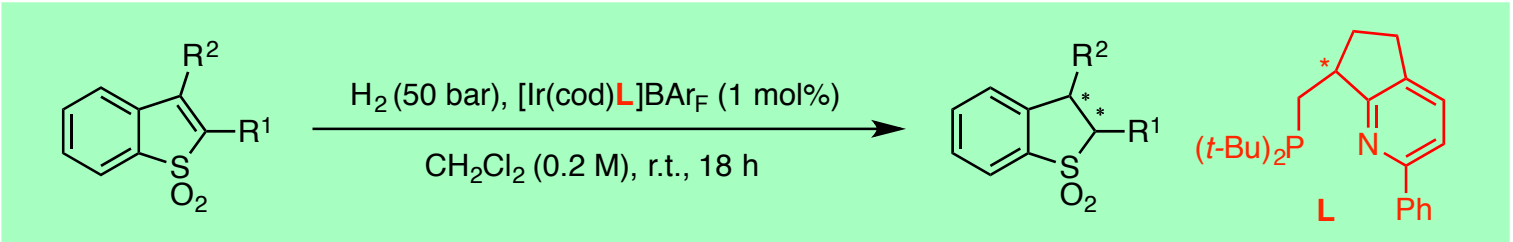


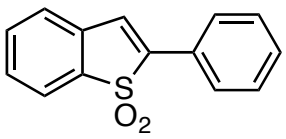
>99% conv.
92% ee

Chem. Eur. J. **2015**, *21*, 1482.

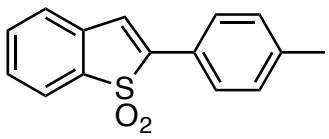
Stefan Kaiser, Larissa Pauli

Asymmetric hydrogenation of Benzothiophene dioxides

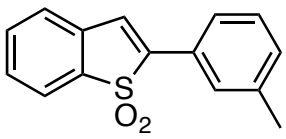




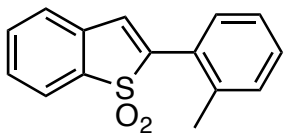
97% conv., 97% ee



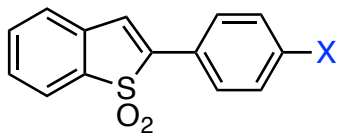
95% conv., 98% ee



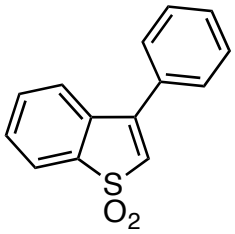
99% conv., 97% ee



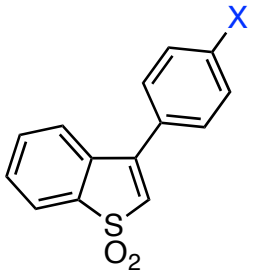
25% conv., 99% ee



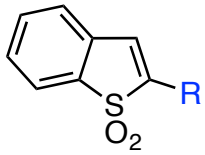
X = F: 81% conv., 98% ee
X = OMe: 99% conv., 99% ee



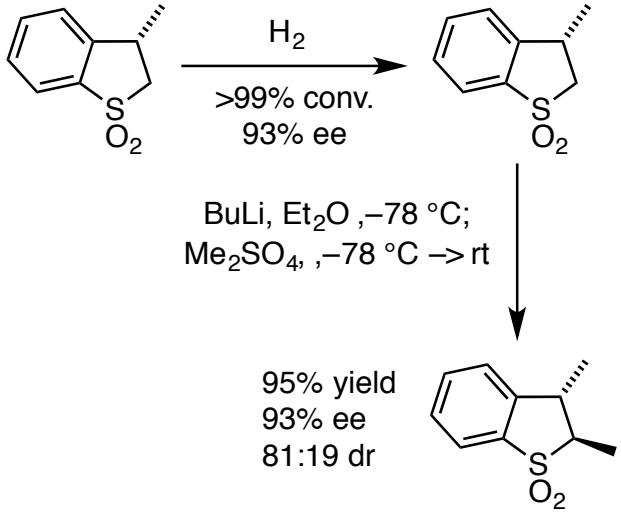
97% conv., 96% ee



X = F: 81% conv., 98% ee
X = OMe: 99% conv., 99% ee

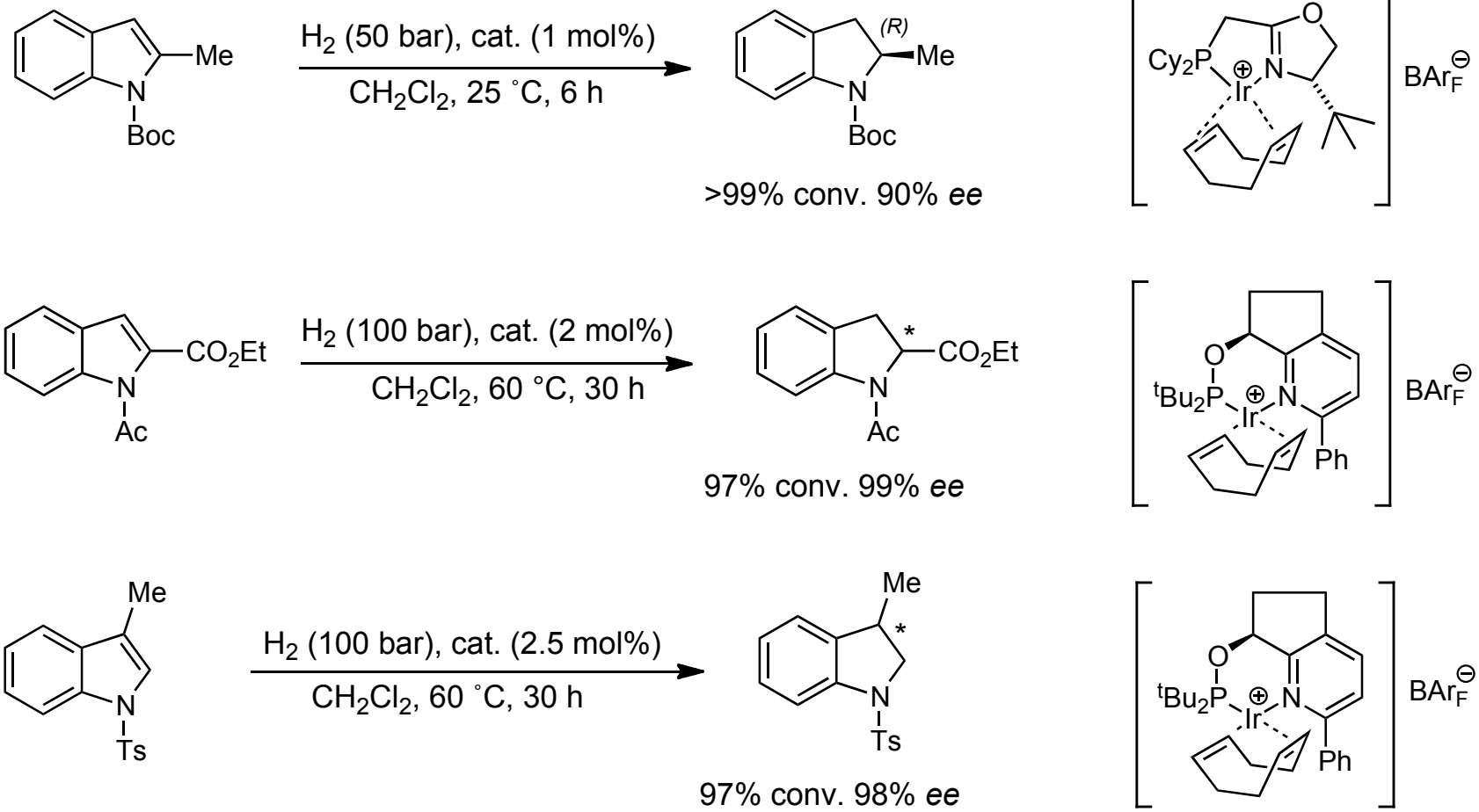


R = Me: >99% conv., 92% ee
R = Et: 95% conv., 84% ee*)
R = iPr: 75% conv., 84% ee
*) 2 bar H_2



Paolo Tosatti, A. P., *Angew. Chem. Int. Ed.* **2017**, *56*, 4579

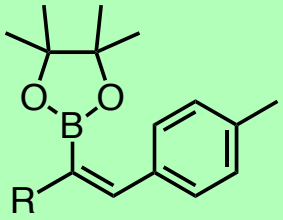
Asymmetric hydrogenation of indoles



Alejandro Baeza

Hydrogenation of Alkenylboranes

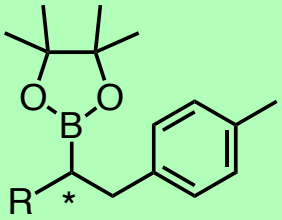
Rh(P^P): J. Morken, *JACS* **2004**, *126*, 15338, *Org. Lett.* **2006**, *8*, 2413. Ir(P^N): P. Andersson, *Chem. Commun.* **2009**, 5996.



1 mol% **cat**

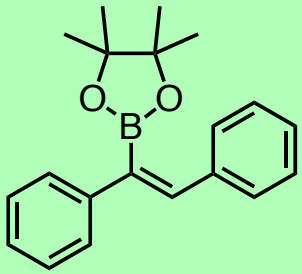
50 bar H_2, rt

CH_2Cl_2

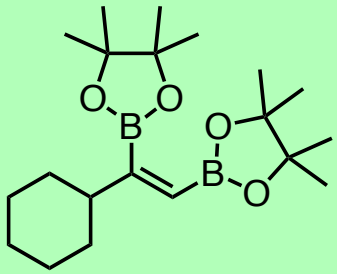


R = *n*-Hexyl: >99% conv., 95% ee

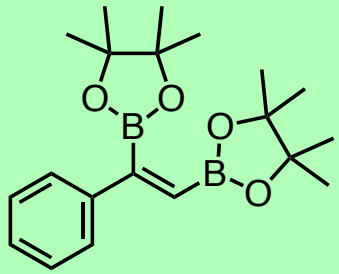
R = Cyclohexyl: >99% conv., 97% ee



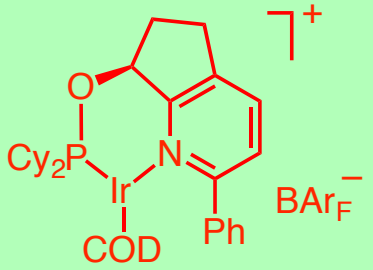
98% conv., 99% ee

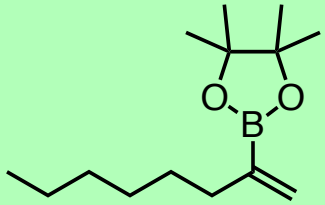


>99% conv., 95% ee



>99% conv., 98% ee

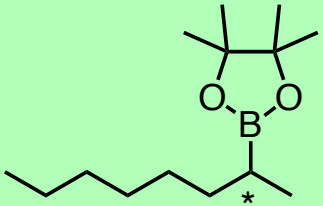




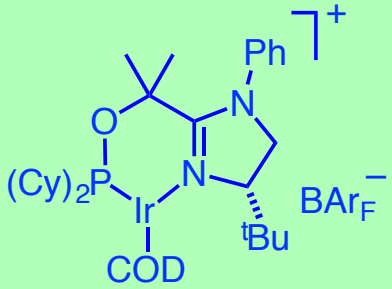
0.1 mol% **cat**

2 bar H_2,–20 °C

CH_2Cl_2

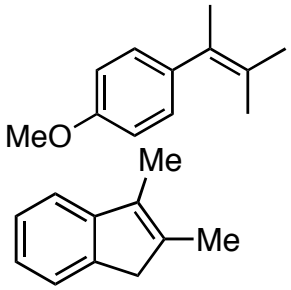


>99% conv., 95% ee



Adnan Ganic, A. P., *Chem. Eur. J.* **2012**, *18*, 6724

Tetrasubstituted Olefins

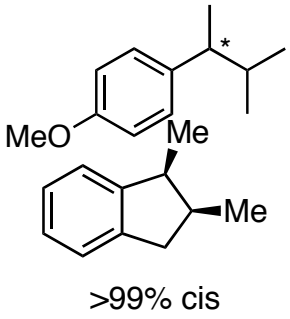


2 mol% cat. **Ir-1**, H_2

CH_2Cl_2, rt

2 mol% cat. **Ir-2**, H_2

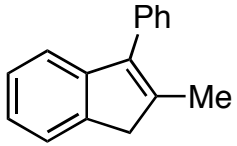
CH_2Cl_2, rt



>99% cis

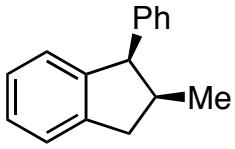
50 bar: 93% ee, >99% conv., 3 h
5 bar: 96% ee, >99% conv., 8 h
1 bar: 97% ee, >99% conv., 3 h

50 bar: 86% ee, >99% conv., 4 h
5 bar: 94% ee, >99% conv., 8 h



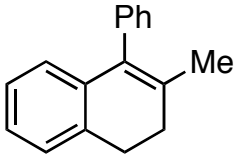
2 mol% cat. **Ir-2**, H_2

CH_2Cl_2, rt



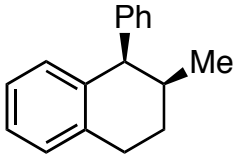
>99% cis

50 bar: 96% ee, 92% conv., 4 h
5 bar: 94% ee, 78% conv., 8 h

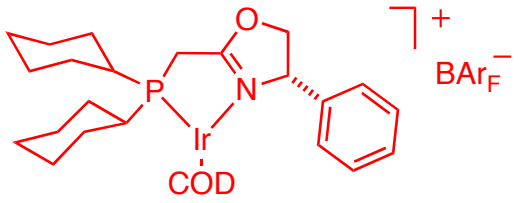


2 mol% cat. **Ir-3**, H_2

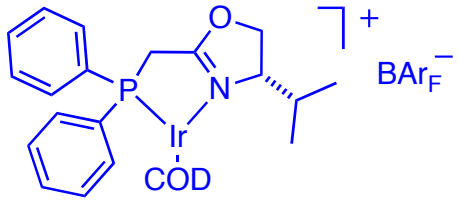
CH_2Cl_2, rt



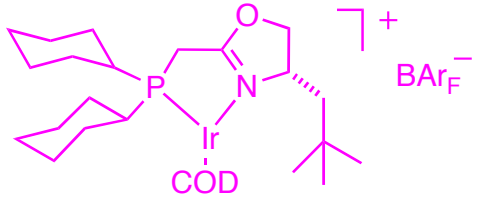
50 bar: 91% ee, 32% conv., 4 h



Ir-1

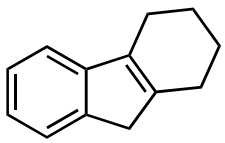


Ir-2



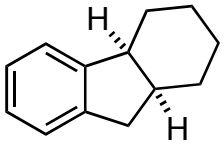
Ir-3

Eva Neumann, Marcus Schrems

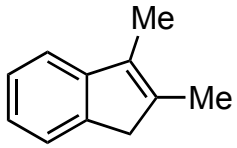


Ir-4, 50 bar H_2

CH_2Cl_2, rt, 4h

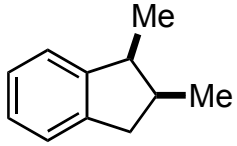


2.0 mol% cat.:	94% ee, >99% conv.
1.0 mol% cat.:	93% ee, >99% conv.
0.5 mol% cat.:	93% ee, >99% conv.
0.1 mol% cat.:	90% ee, >99% conv.



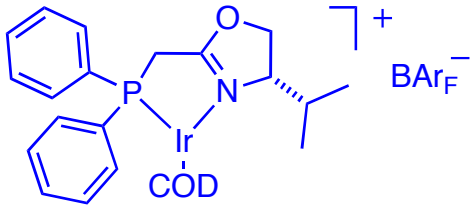
Ir-2, 50 bar H_2

CH_2Cl_2, rt, 4h

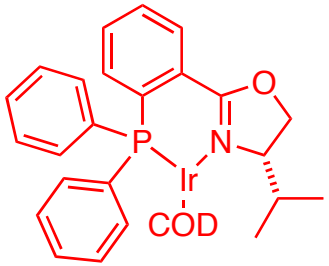


>99% cis

2.0 mol% cat.:	86% ee, >99% conv.
1.0 mol% cat.:	86% ee, >99% conv.
0.5 mol% cat.:	83% ee, >99% conv.
0.1 mol% cat.:	79% ee, 91% conv.



Ir-2

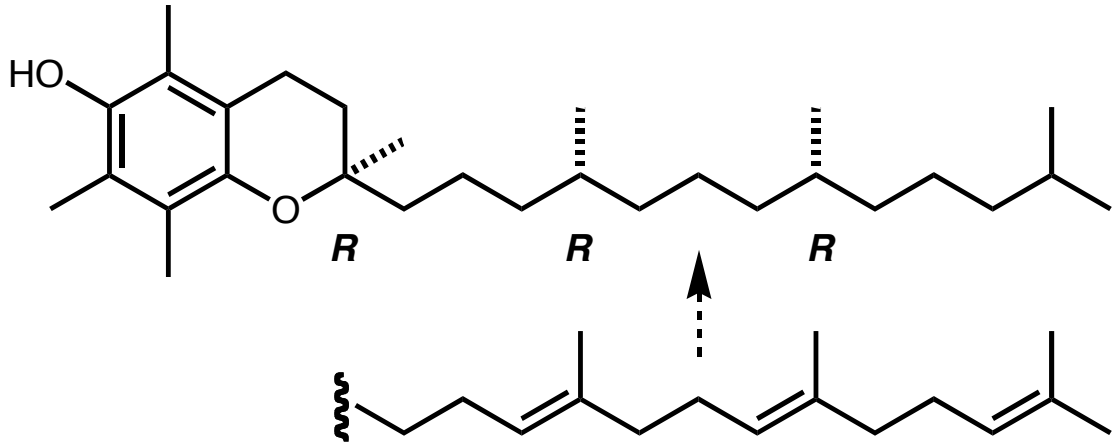


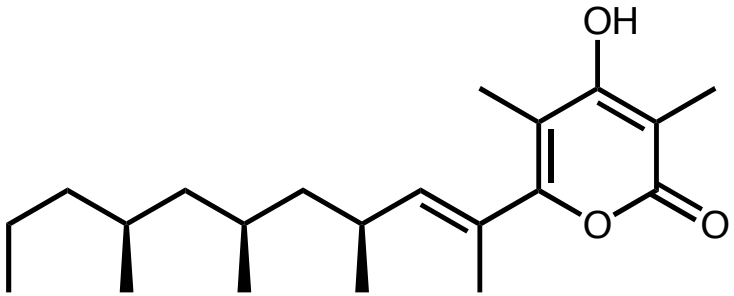
Ir-4

Marcus Schrems

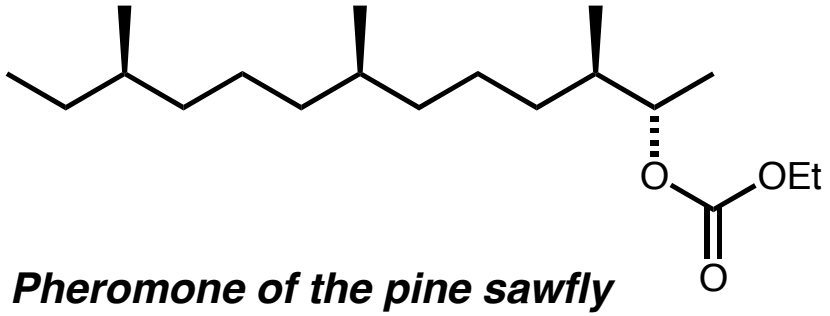
Trialkyl-substituted C=C bonds, no heteroatoms, no aryl groups?

α-Tocopherol (vitamin E)

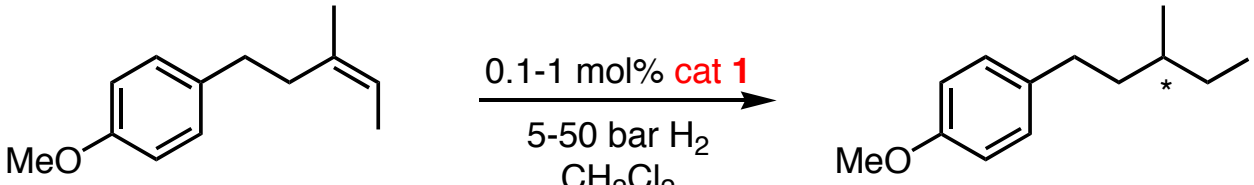




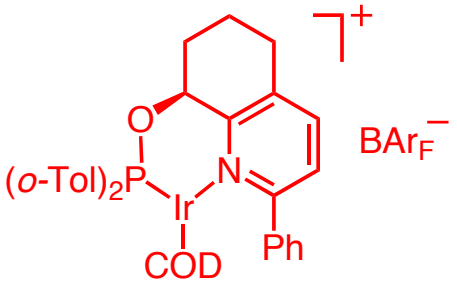
Pectinatone (anti-bacterial, anti-fungal, cytotoxic activity)



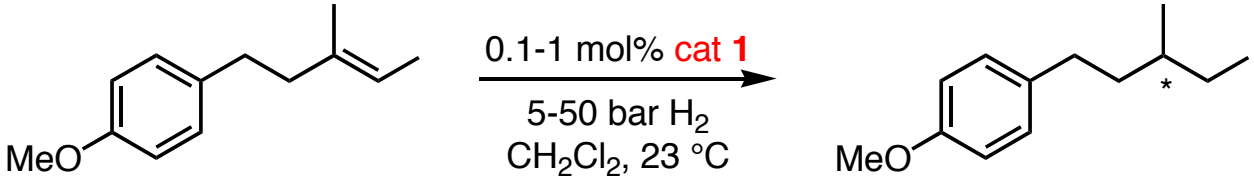
Pheromone of the pine sawfly



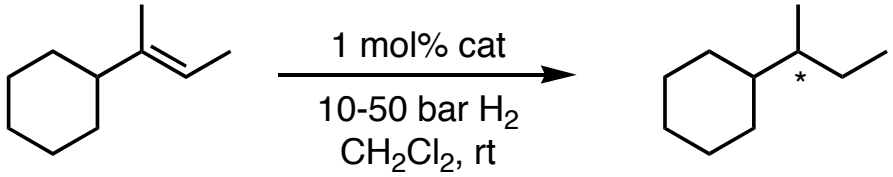
50 bar	98% ee
4 bar	98% ee
1 bar	94% ee



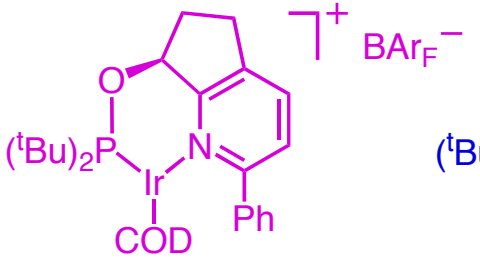
1



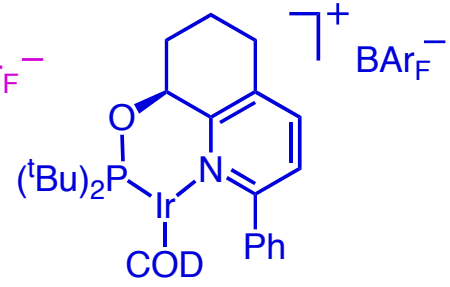
50 bar	95% ee
25 bar	95% ee
5 bar	94% ee



cat **2**	50 bar	97% ee
	10 bar	97% ee
cat **3**	50 bar	97% ee
	25 bar	93% ee
	10 bar	86% ee



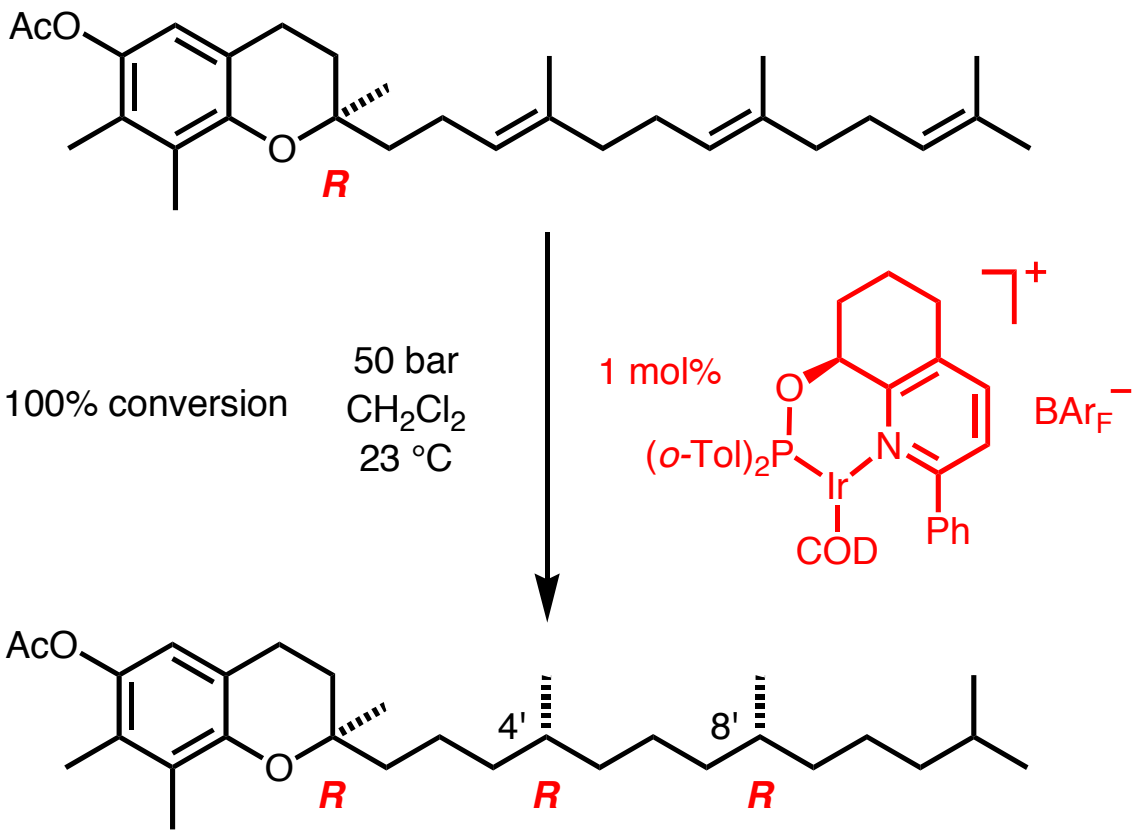
2



3

Sharon Bell
Aie Wang

(*R,R,R*)-Tocopherol (Vitamin E)

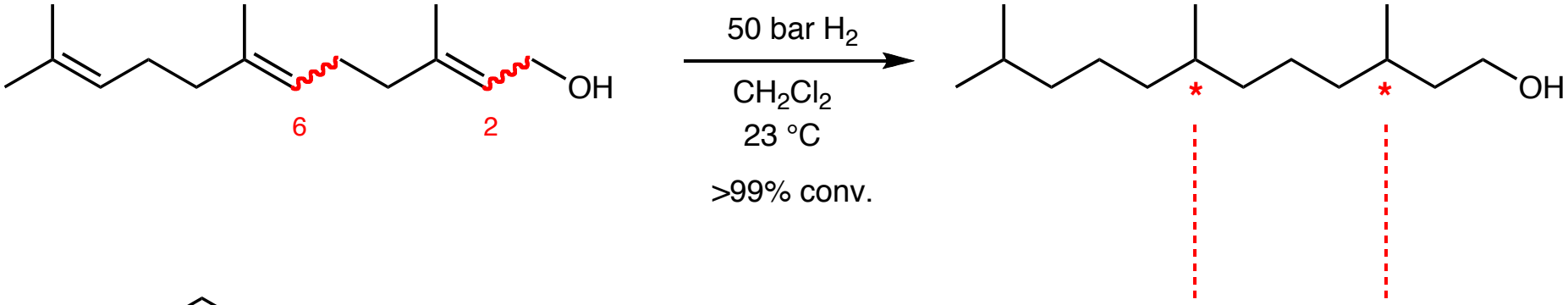


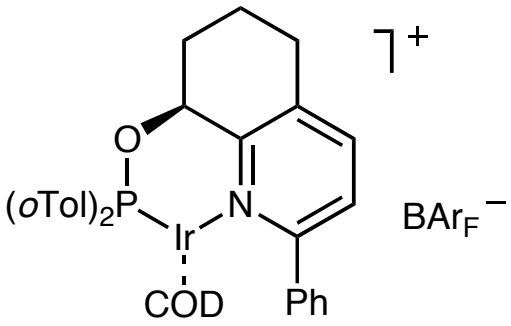
99% *RRR*; < 0.3% *RRS*; < 0.3% *RSR*; < 0.4% *RSS*

GC analysis: Vecchi et al. *Helv. Chim. Acta* **1990**, *73*, 782.

S. Bell, B. Wüstenberg, S. Kaiser, F. Menges, T. Netscher, A. P. *Science* **2006**, *311*, 642.

Enantio- and diastereoselective hydrogenation of farnesol





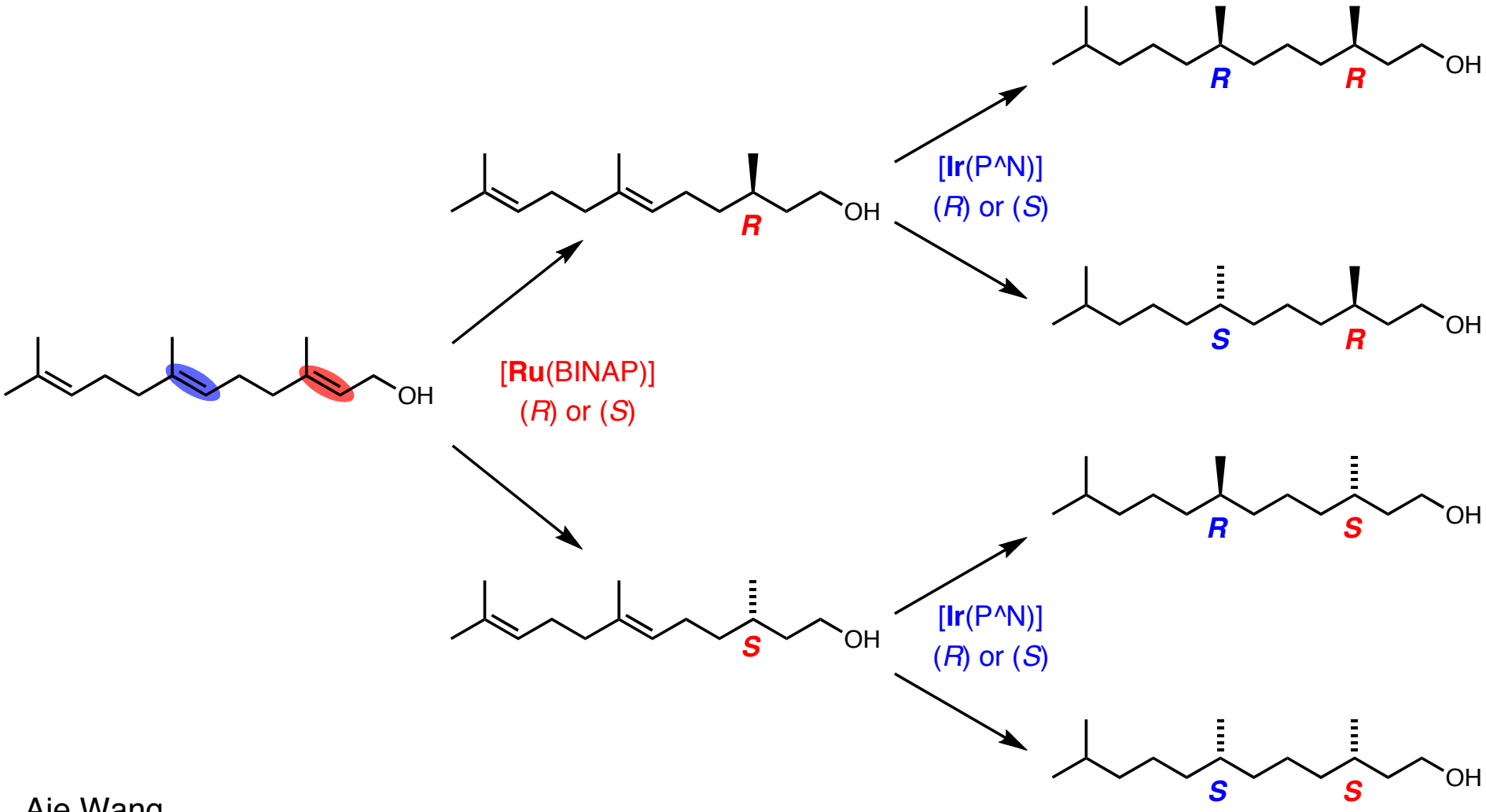
0.1-1 mol%

2*E*, 6*E*	**91% 2*R*, 6*R* (>99% ee)**	**99:1**	**94:6**
2*Z*, 6*E*	**95% 2*S*, 6*R* (>99% ee)**	**98:2**	**97:3**
2*E*, 6*Z*	**93% 2*R*, 6*S* (>99% ee)**	**98:2**	**95:5**
2*Z*, 6*Z*	**96% 2*S*, 6*S* (>99% ee)**	**98:2**	**98:2**

Stereoselective synthesis of farnesol isomers: J. S. Ju, T. S. Kleckley, D. F. Wiemer, *Org. Lett.* **2005**, *7*, 4803.

Aie Wang

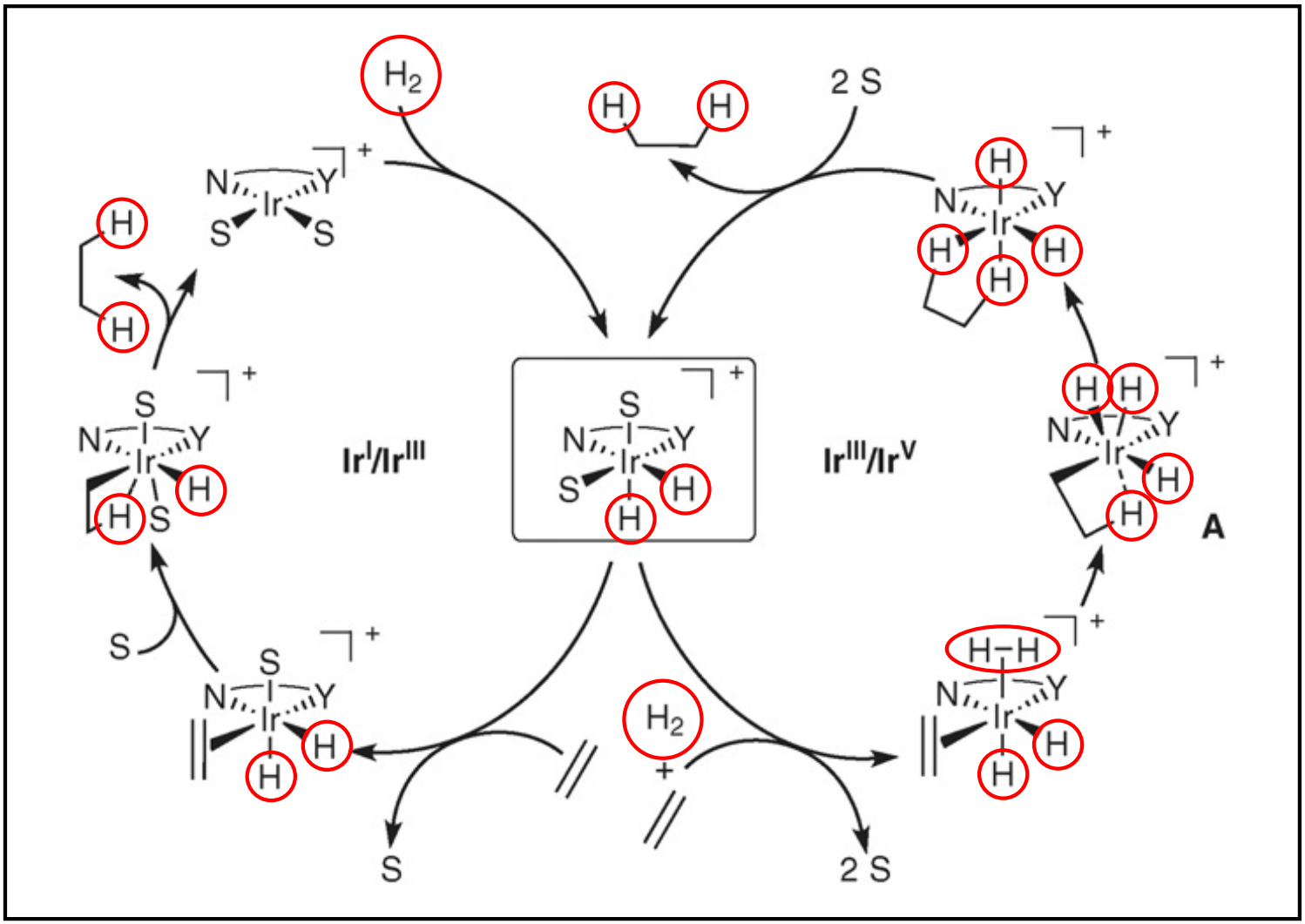
Sequential hydrogenation using Ru and Ir catalysts



Aie Wang

Mechanistic Studies

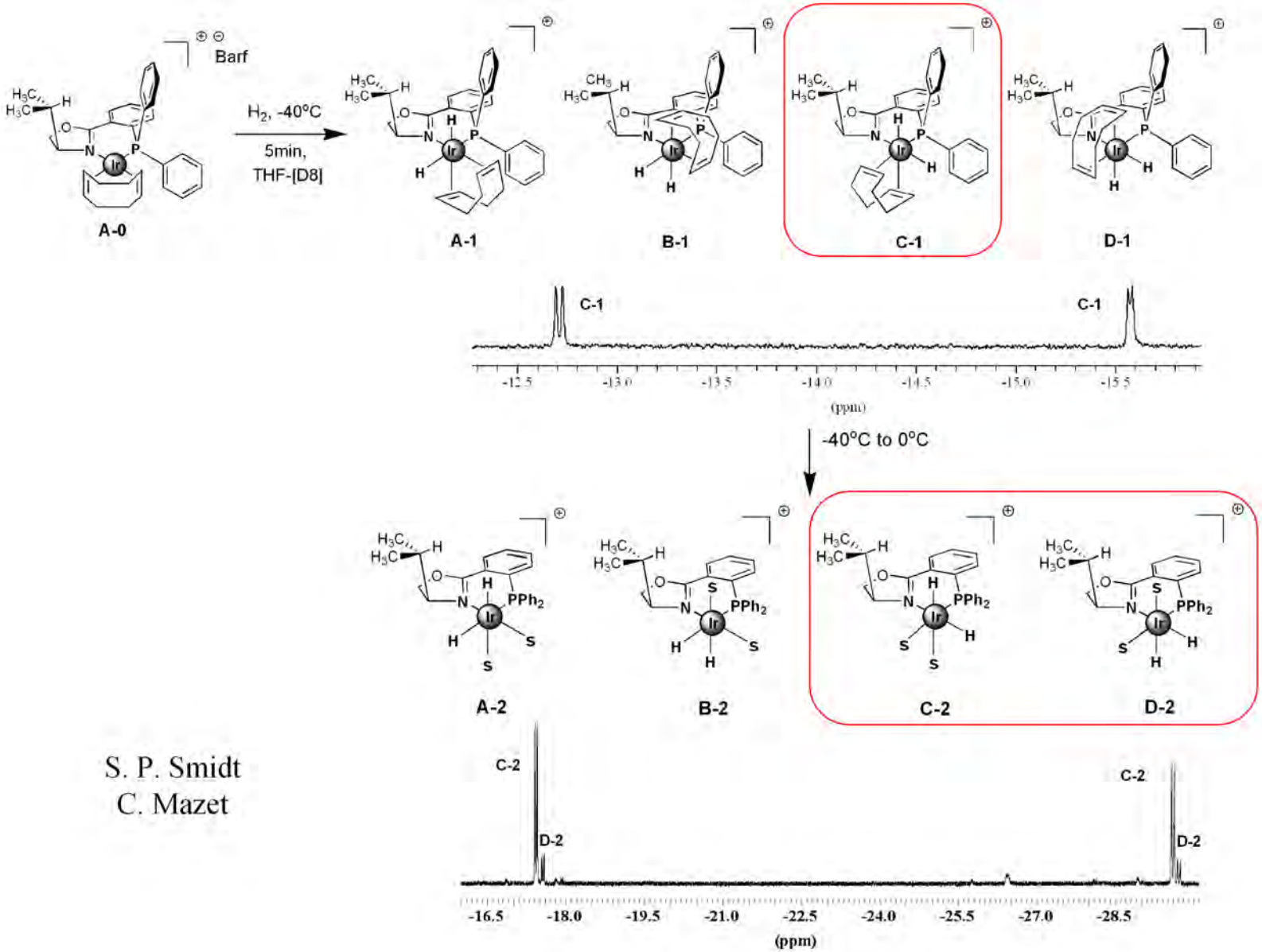
Proposed catalytic cycles



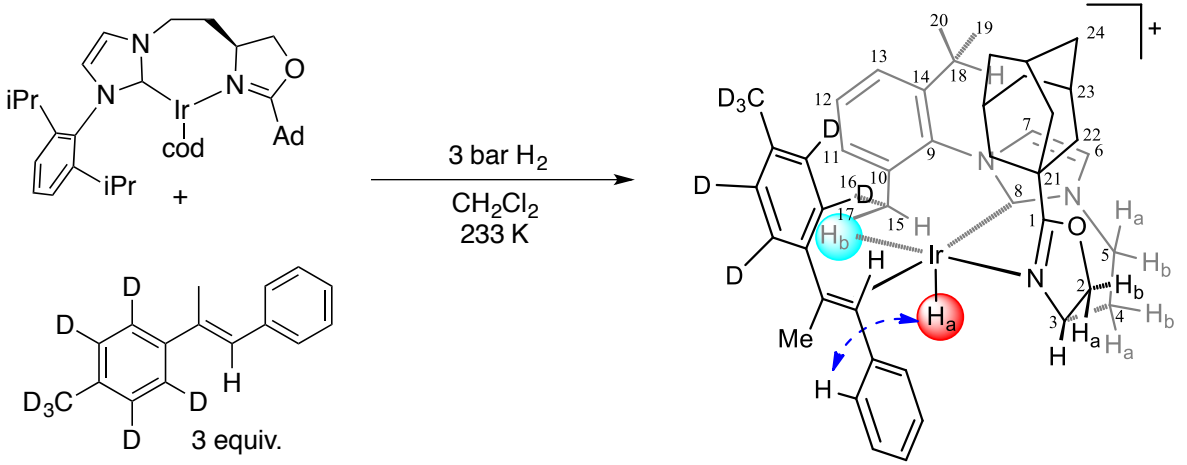
P. Brandt, P. G. Andersson *et al*, *Chem. Eur. J.* **2003**, *9,* 339.

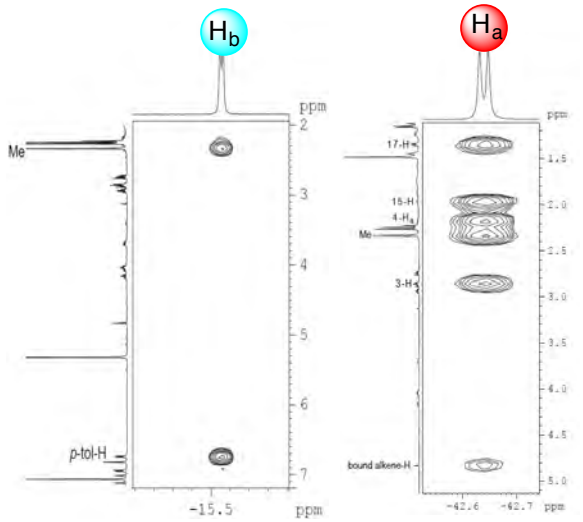
K. Burgess, M. B. Hall *et al.*, *JACS* **2004,** *126,* 16688.

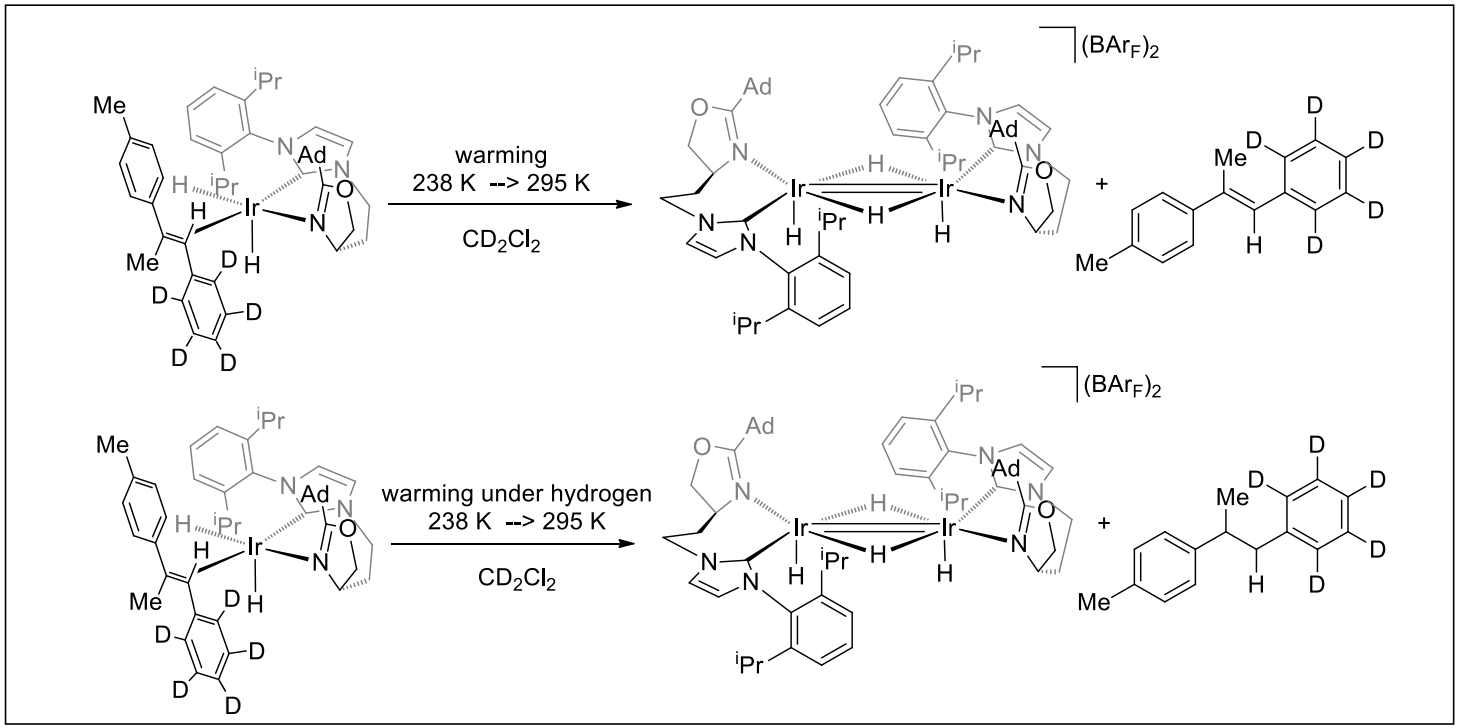
Activation of the precatalyst



S. P. Smidt
C. Mazet

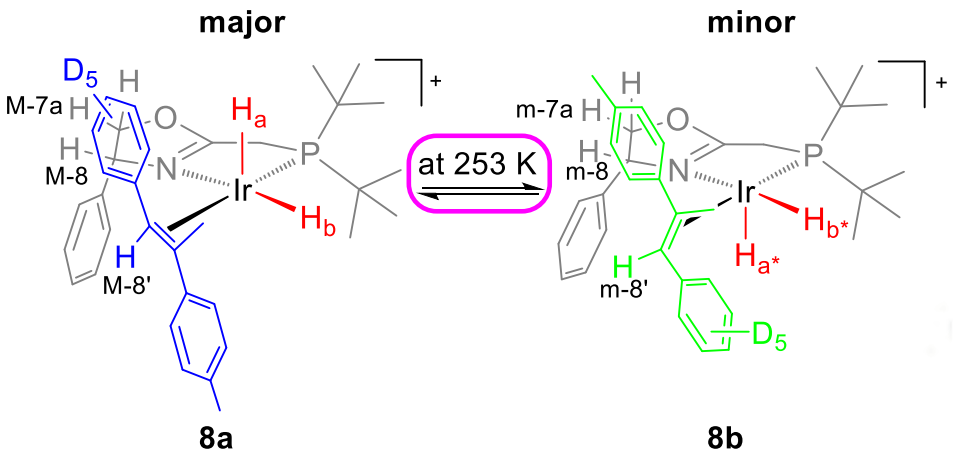


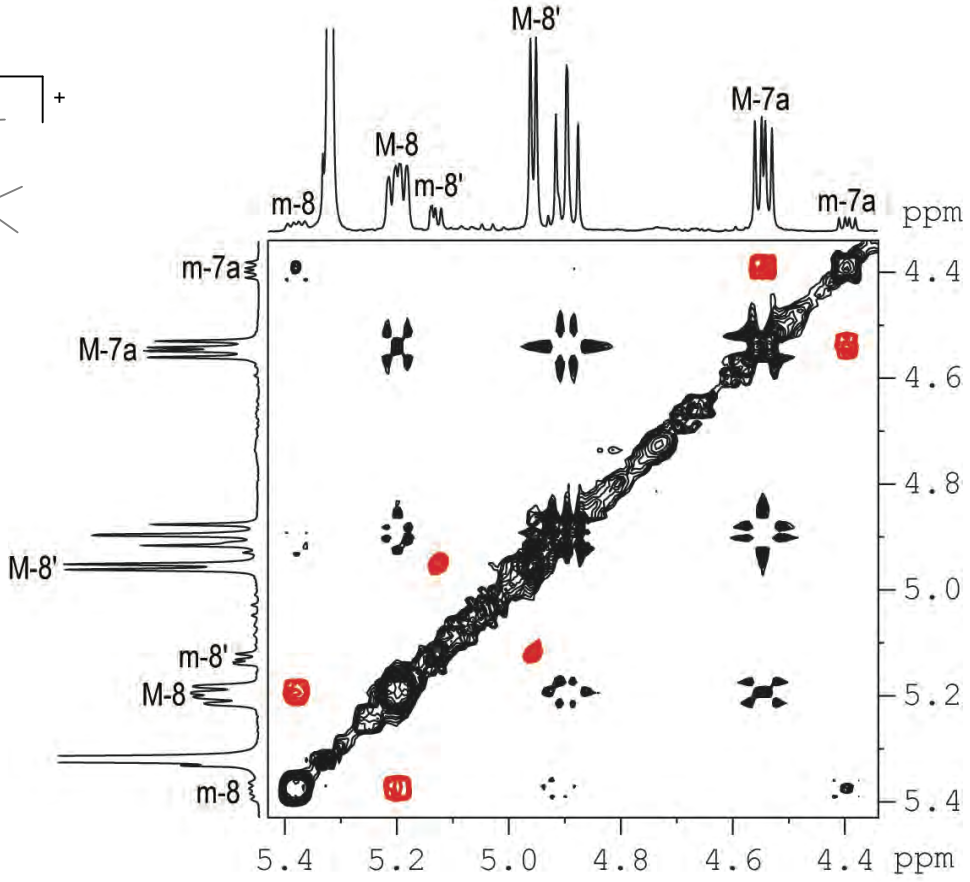




Stefan Gruber

Rapid enantioface exchange of Ir dihydride alkene complexes



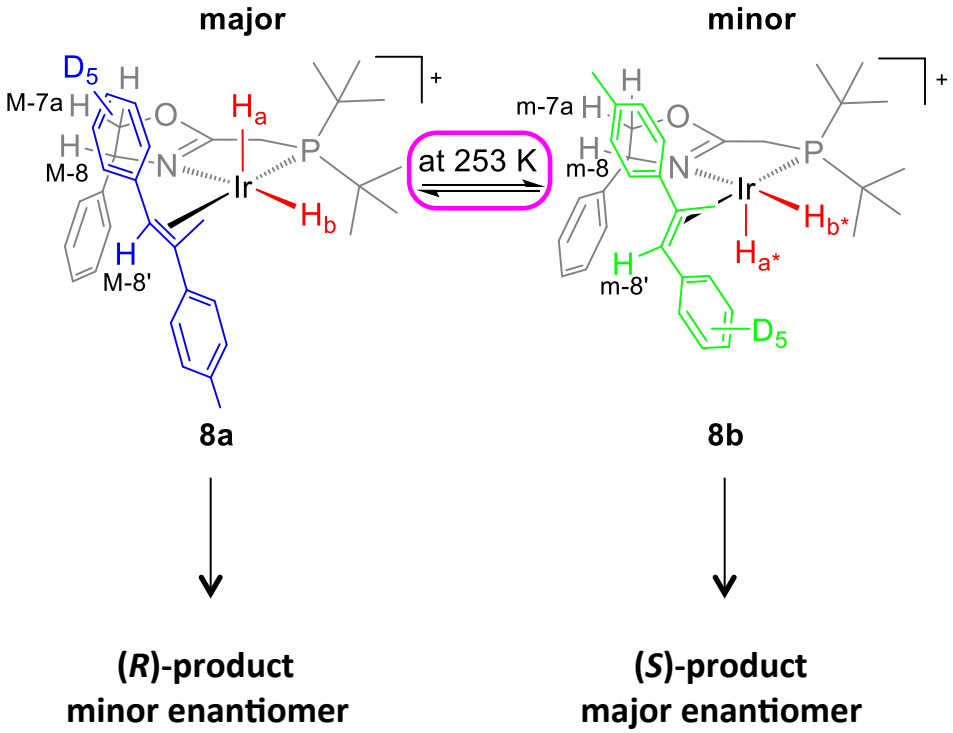


Section of the 2D NOESY spectrum showing the exchange cross-peaks (253 K, 500 MHz, CD_2Cl_2).

Stefan Gruber

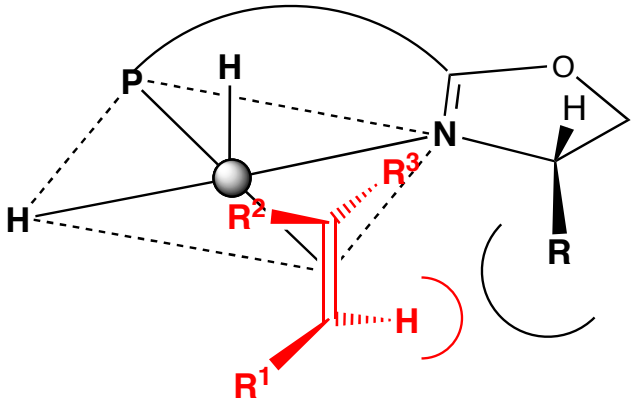
Angew. Chem. Int. Ed. **2014**, *53*, 1896.

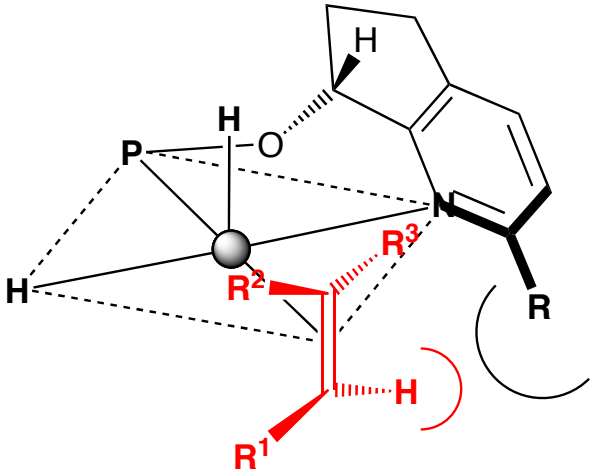
Rapid enantioface exchange of Ir dihydride alkene complexes



Stefan Gruber

Mechanistic Model

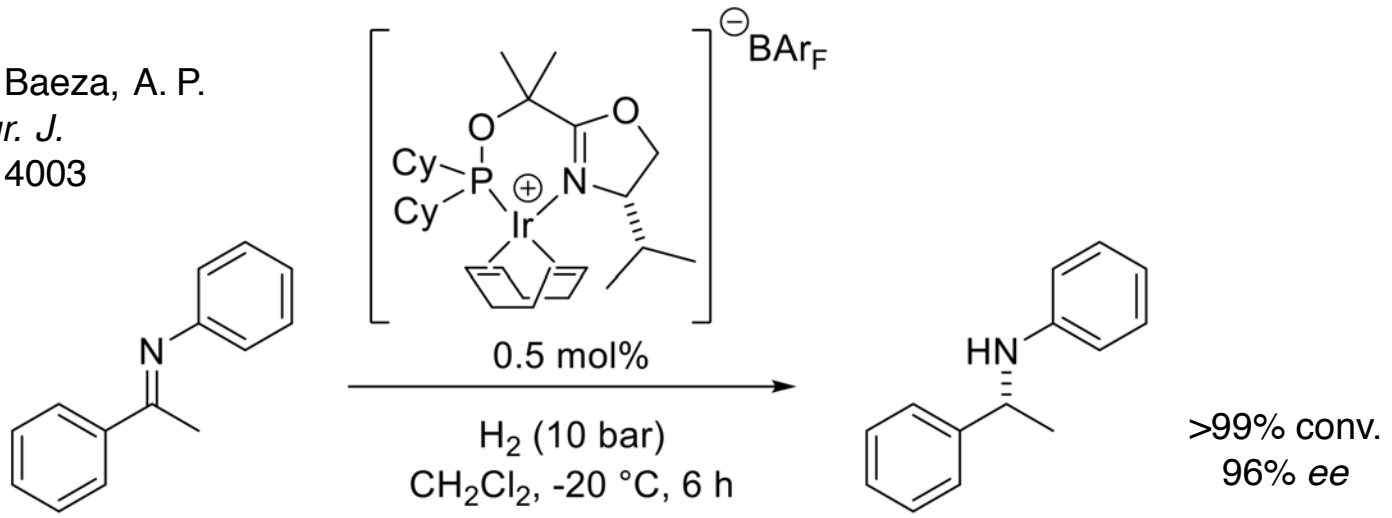




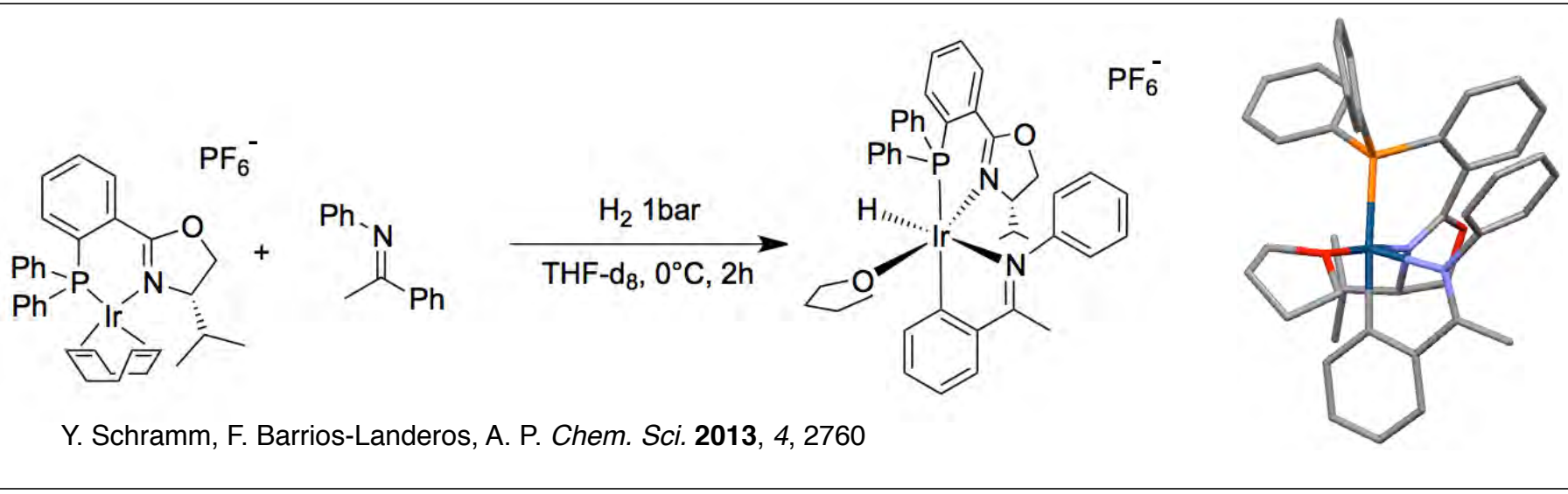
Computational studies: Pher Andersson (Uppsala University)
Kevin Burgess (Texas A&M)
Kathrin Hopmann (University of Tromsø)
Markus Meuwly (University of Basel))

Imine hydrogenation: unexpected mechanistic results

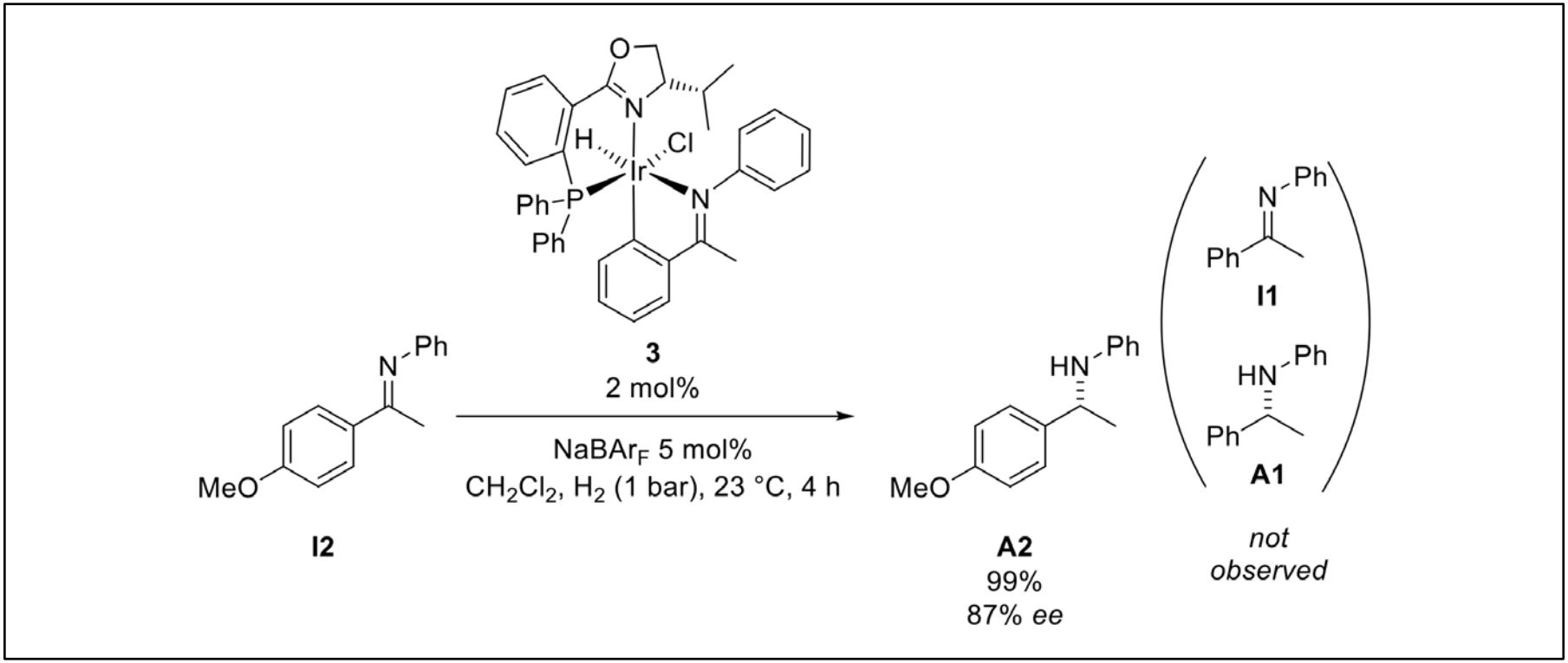
Alejandro Baeza, A. P.
Chem. Eur. J.
2010, *16*, 4003

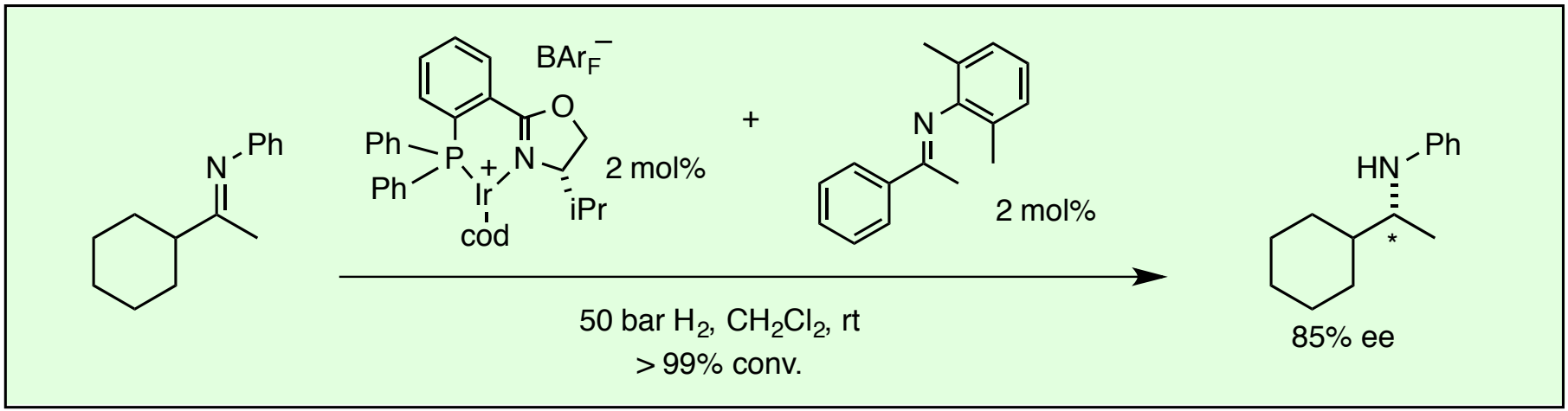


>99% conv.
96% *ee*



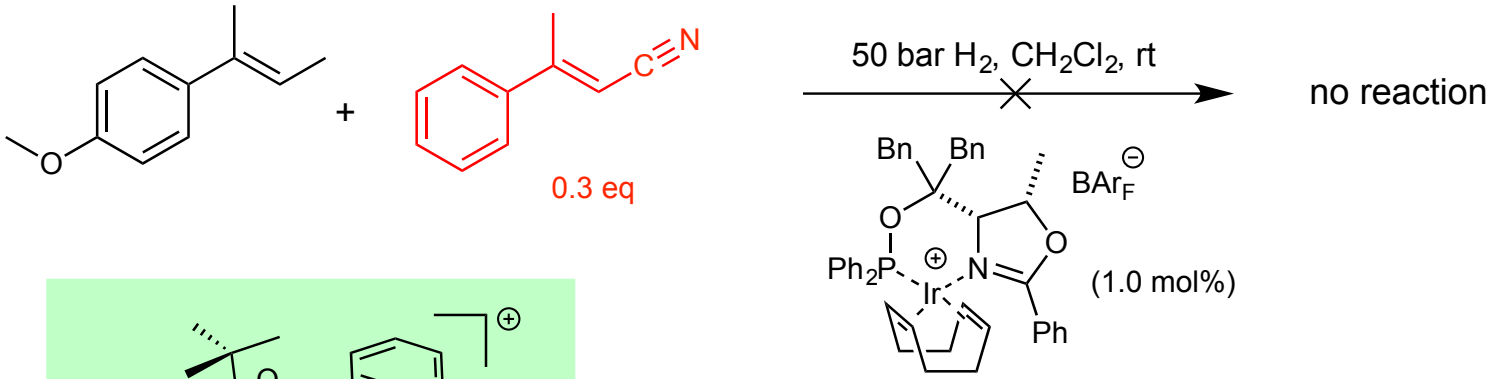
Y. Schramm, F. Barrios-Landeros, A. P. *Chem. Sci.* **2013**, *4*, 2760

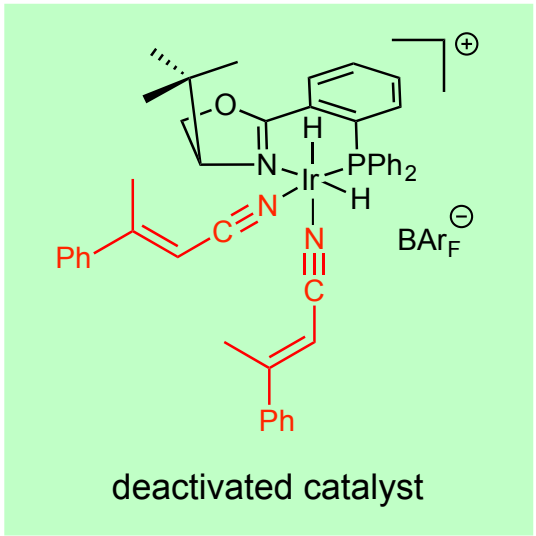




York Schramm

α,β-Unsaturated Nitriles





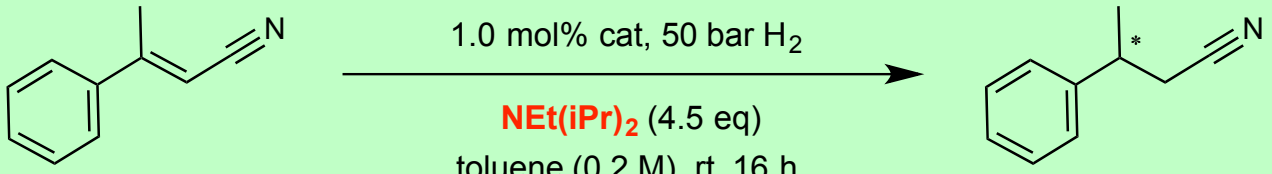
deactivated catalyst

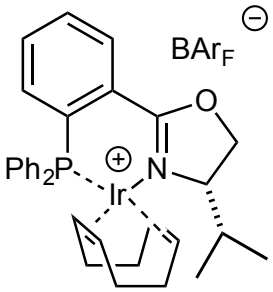
Marc-André Müller

Hydrogenation of electrophilic C=C bonds with base-activated Ir-PHOX catalysts:
V. Semeniuchenko, V. Khilya, U. Groth, *Synlett* **2009**, 271

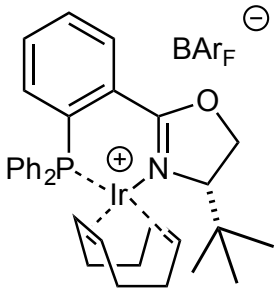
Addition of $NEt(iPr)_2$ ⟹ **?**

α,β-Unsaturated Nitriles

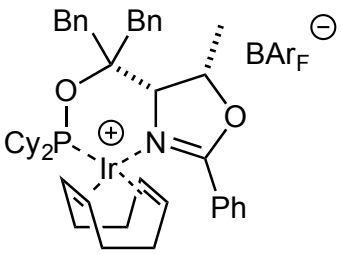




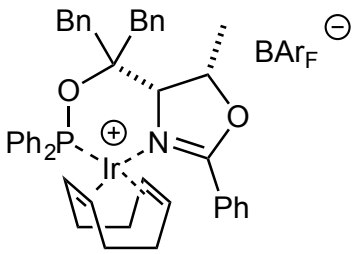
1
0.3% conv.



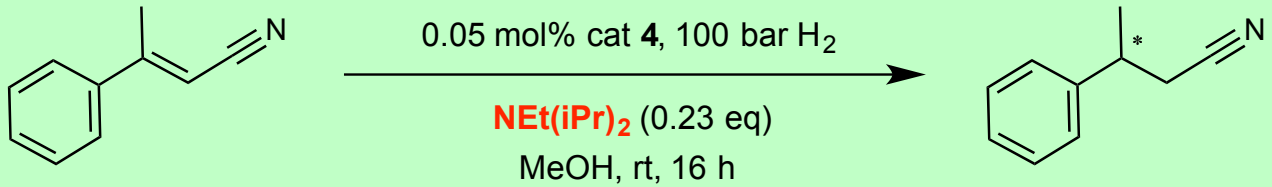
2
10% conv.; 34% *ee*



3
8% conv.; 47% *ee*



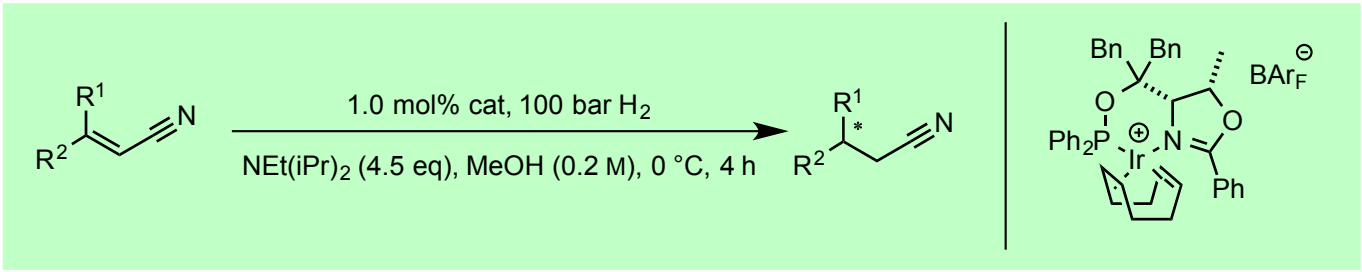
4
98% conv.; 94% *ee*

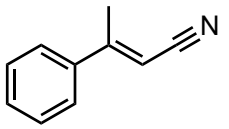


>99% conv.; 96% *ee*

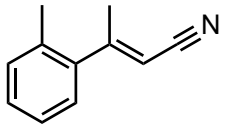
Marc-André Müller

α,β-Unsaturated Nitriles

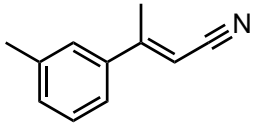




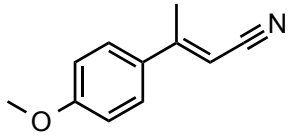
conv. = >99%
ee = 98%



conv. = 71%
ee = 82%



conv. = >99%
ee = 97%



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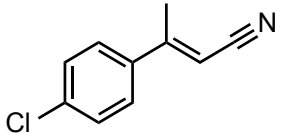
ee = 96%



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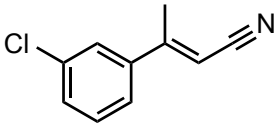
ee = 97%



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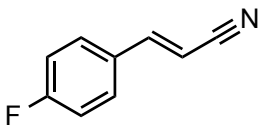
ee = 98%



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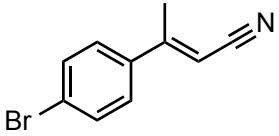
ee = 96%



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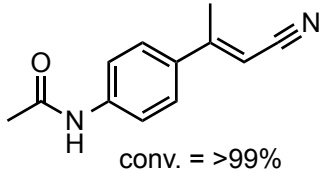
ee = 97%



conv. = >99%
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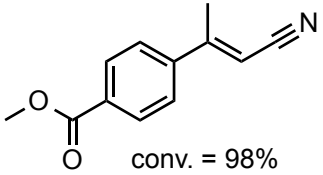

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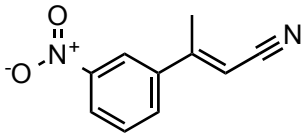
ee = 98%



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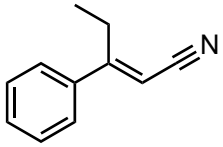

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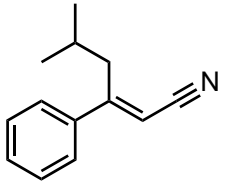

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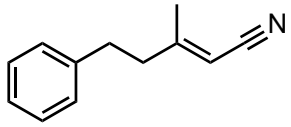

conv. = >99%
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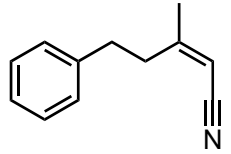
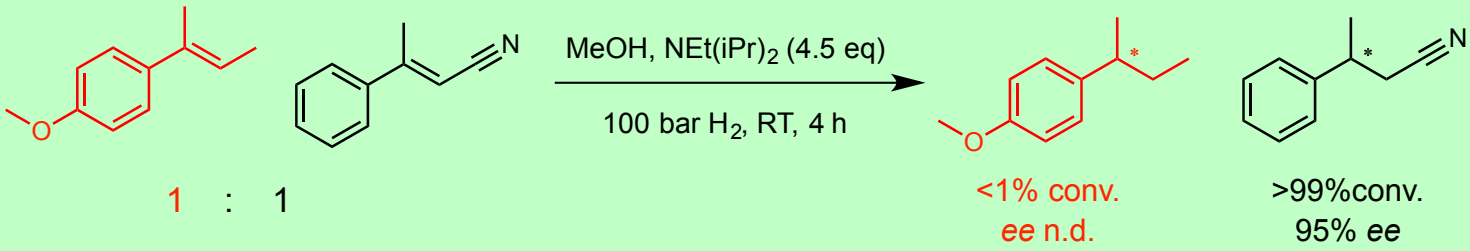


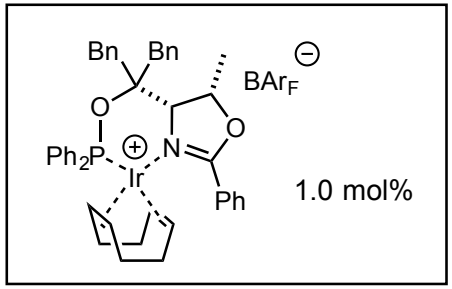
conv. = >99%
ee = 82%

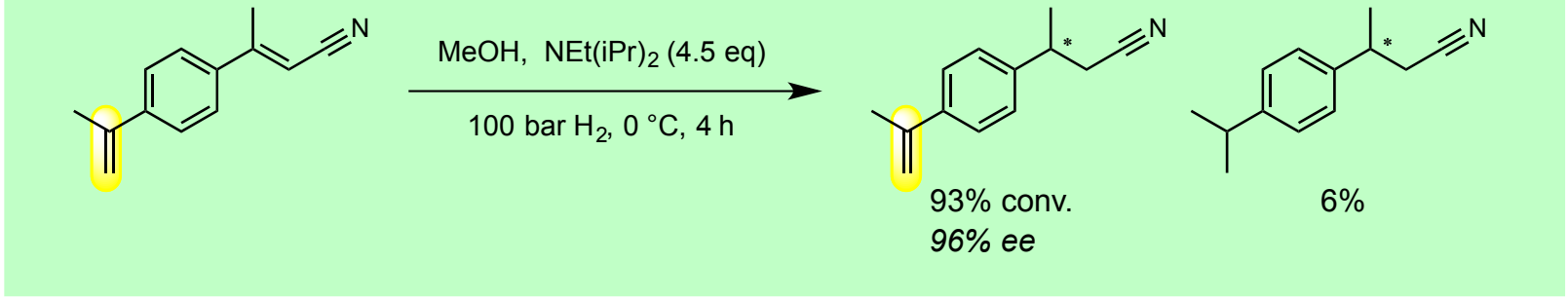
Angew. Chem. Int. Ed. **2014**, *53*, 8668.

Marc-André Müller

Selective Hydrogenationof Cyano-Substituted C=C Bonds



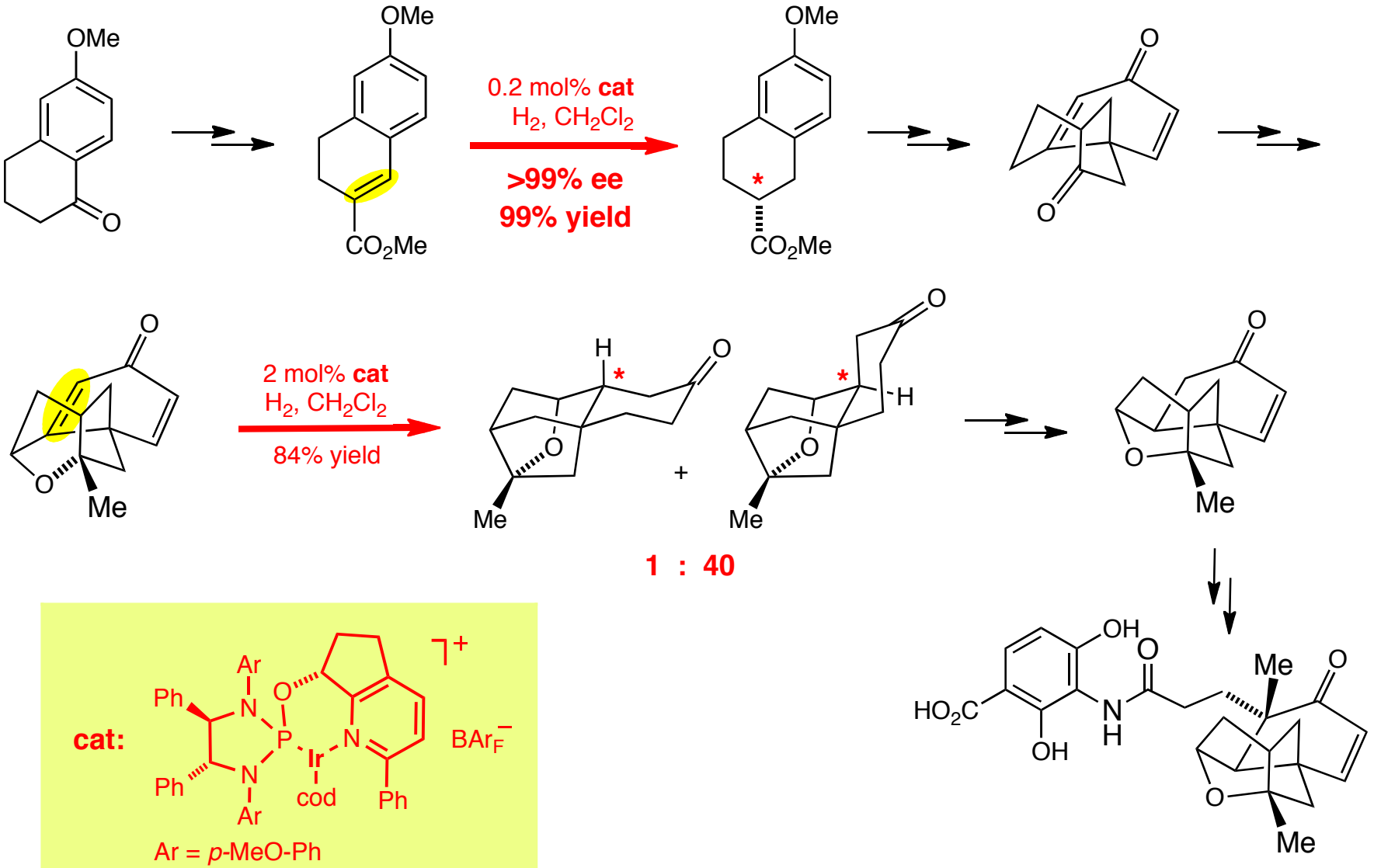




Marc-André Müller

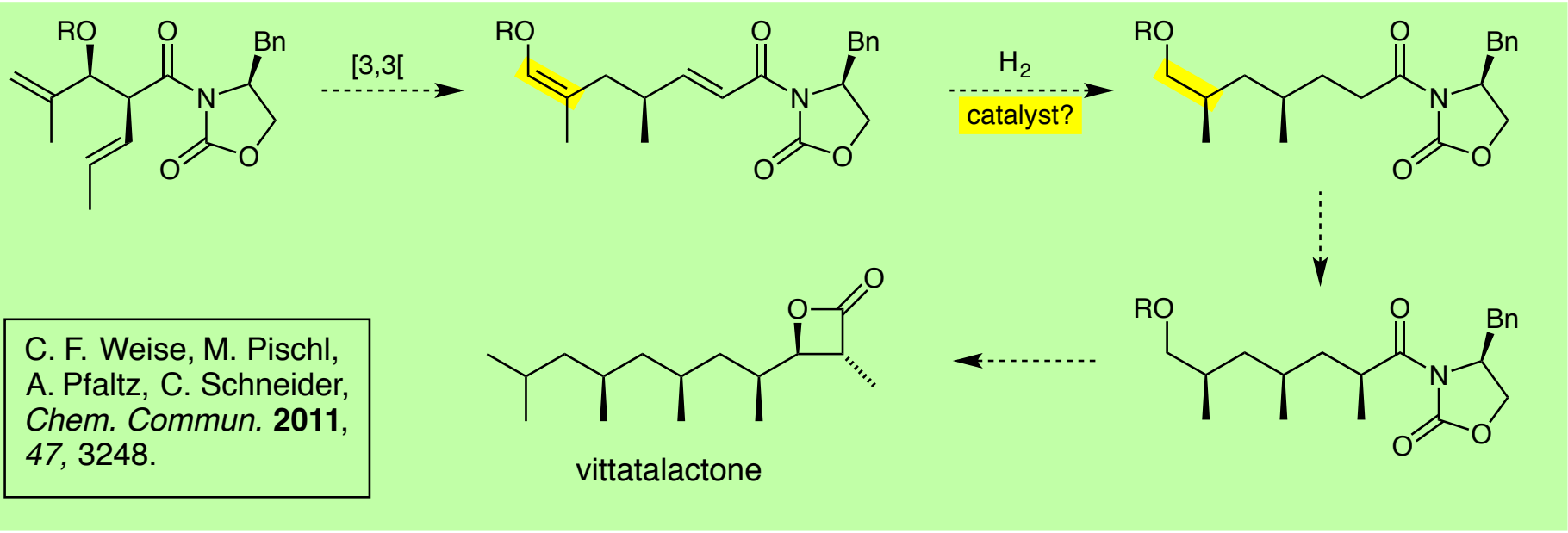
Applications in the Synthesis of Natural Products

Synthesis of Platensimycin

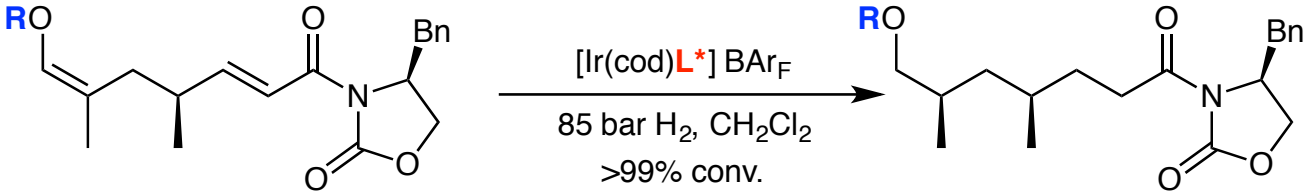


Konrad Tiefenbacher & Johann Mulzer, Lars Tröndlin & A. P.

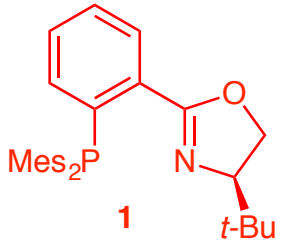
Synthesis of the Cucumber Beetle Pheromone Vittatalactone



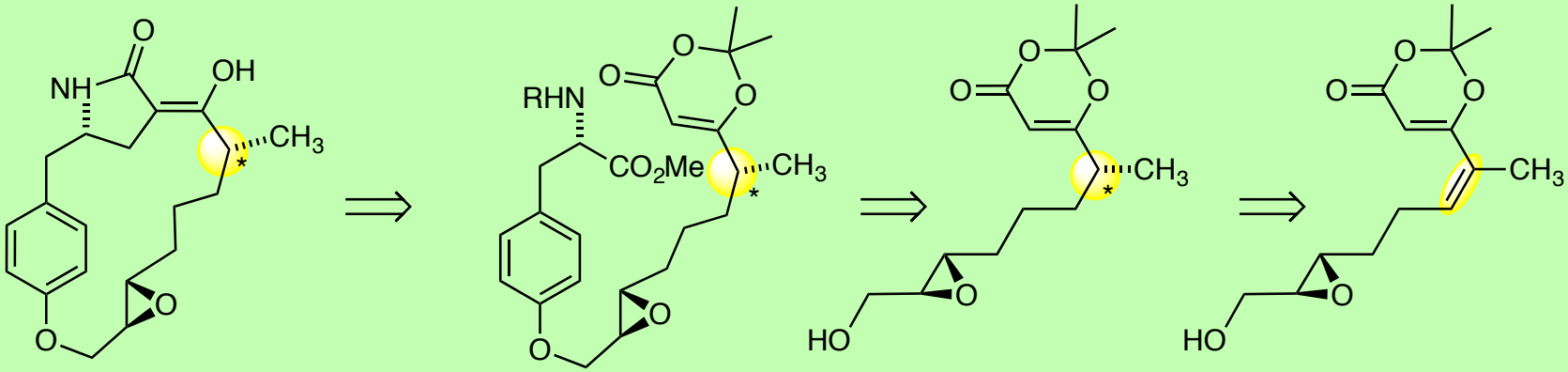
C. F. Weise, M. Pischl, A. Pfaltz, C. Schneider, *Chem. Commun.* **2011**, *47,* 3248.



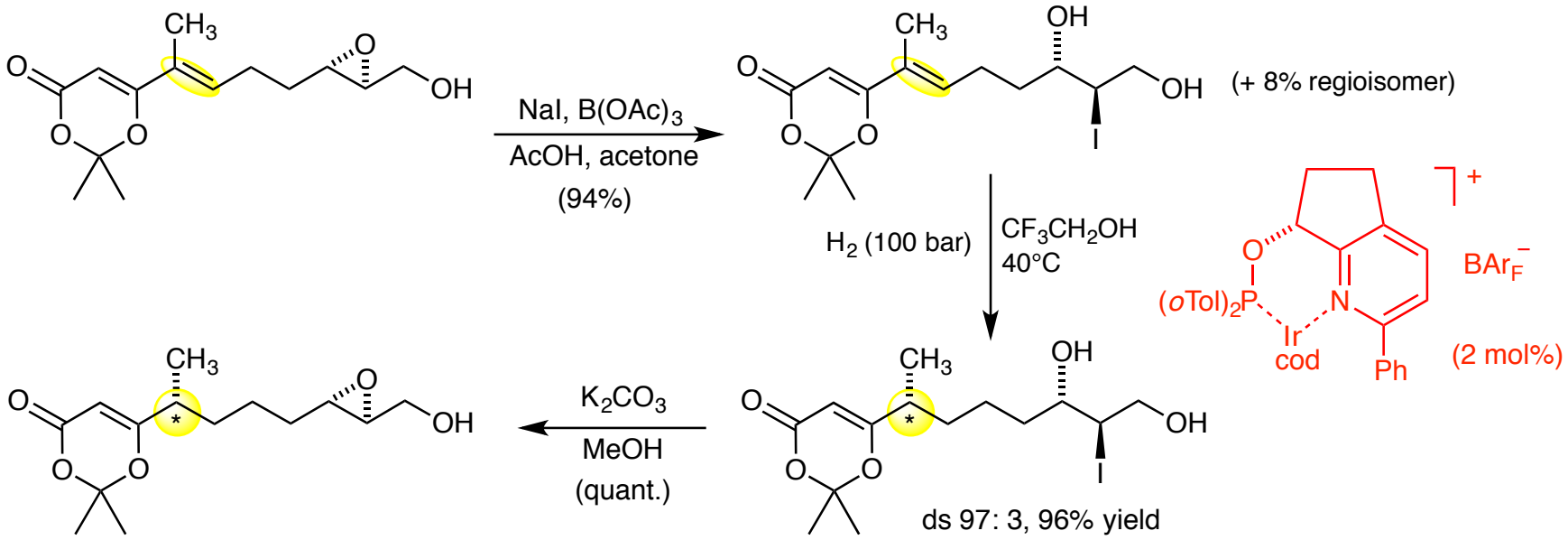
R	L*	*syn/anti*
COPh	**1**	97 : 3
COPh	*ent*-**1**	4 : 96
CONH*t*-Bu	**1**	97 : 3
CONH*t*-Bu	*ent*-**1**	2 : 98



Total Synthesis of Macrocidin A



T. Yoshinari, K. Ohmori, M. G. Schrems, A. Pfaltz, K. Suzuki, *Angew. Chem. Int. Ed.* **2010**, *89*, 881



Tomohiro Yoshinari, Marcus Schrems

Patrick Schnider
Roger Prétôt
Guido Koch
Dr. Olivier Legrand
Dr. Andrew Lightfoot
Jörg Blankenstein
Frederik Menges
Steven McIntyre
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Dr. Hans-Ulrich Blaser, Dr. Martin Studer
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(Solvias AG, Basel)

Dr. Thomas Netscher, Dr. Werner Bonrath
(DSM Nutritional Products)

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Solvias AG, Basel - DSM Nutritional Products